SYNTHESIS AND *INVITRO* ANTI-CANCER EVALUATION OF SOME NOVEL 2, 3 DISUBSTITUTED THIAZOLIDINONES

A Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY,

CHENNAI- 600 032

In partial fulfillment of the award of the degree of

MASTER OF PHARMACY

IN

Branch-II – PHARMACEUTICAL CHEMISTRY

Submitted by

Name: PRABHA.B

Reg.No: 261515202

Under the Guidance of

Dr. M. SENTHILRAJA, M. Pharm., Ph.D., FIC,

DEPARTMENT OF PHARMACEUTICAL CHEMISTRY

J.K.K. NATTARAJA COLLEGE OF PHARMACY

KUMARAPALAYAM – 638183

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EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"Synthesis and *in-vitro* anti-cancer evaluation of some novel 2, 3-Disubstituted Thiazolidinones"** submitted by the student bearing **Reg.No: 261515202** to The Tamil Nadu Dr. M. G. R. Medical University, Chennai, in partial fulfillment for the award of degree of **MASTER OF PHARMACY** in the **DEPARTMENT OF PHARMACEUTICAL CHEMISTRY** was evaluated by us during the examination held on……..

Internal Examiner **External Examiner**

CERTIFICATE

This is to certify that the work embodied in this dissertation "**Synthesis and *in-vitro* anti-cancer evaluation of some novel 2, 3 disubstituted thiazolidinones"** submitted to The Tamil Nadu Dr.M.G.R. Medical University, Chennai, was carried out by **Mrs. PRABHA. B [Reg.No:261515202]** for the partial fulfillment of degree of **MASTER OF PHARMACY** in the Department of Pharmaceutical Chemistry under the direct supervision of **Dr. M.SENTHILRAJA, M.Pharm., Ph.D., F.I.C,** Professor, Department of Pharmaceutical Chemistry, J.K.K. Nattraja College of Pharmacy, Kumarapalayam-638183.

Place: Kumarapalayam
Date:

Dr. R. Sambathkumar, M. Pharm., PhD.,
Professor & Principal,
J.K.K. Nattraja College of Pharmacy.
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CERTIFICATE

The work presented in this dissertation entitled **"Synthesis and *in-vitro* anti-cancer evaluation of some novel 2, 3 disubstituted thiazolidinones",** was carried out by me, under the direct supervision of **Dr. M.SENTHILRAJA, M.Pharm.,Ph.D.,FIC,** Professor, Department of Pharmaceutical Chemistry, J.K.K. Nattraja College of Pharmacy, Kumarapalayam.

I further declare that, this work is original and has not been submitted in part or full for the award of any other degree or diploma in any other University.

Place: Kumarapalayam **Mrs. PRABHA .B**

Date: **Reg.No.261515202**

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Mrs.PRABHA.B

Reg.No: (261515202)

DEDICATED TO MY ALMIGHTY, PARENTS, HUSBAND AND GUIDE

CONTENT

CHAPTER -1

INTRODUCTION

Chemistry is a very broad subject, and can justly claim to encompass many aspects of the study of biological molecules. To most researchers in the cancer fields, the term 'chemistry' is often used in a much narrower way and is synonymous with the synthetic chemistry as a tool for the discovery of anticancer drugs.

1.1. PHARMACEUTICALCHEMISTRY

Pharmaceutical Chemistry is an area of chemistry that deals with the structure, properties and reactions of compounds that contains carbon. Chemists in general and organic chemists in particular can create new molecules never before proposed which, if carefully designed, may have important properties for the betterment of the human experience. One of the main objectives of organic and medicinal chemistry is the design, synthesis and production of molecule having value as human therapeutic agents[1].

The department of pharmaceutical chemistry is to impart in depth knowledge about all the chemical aspects of drugs and natural products, such as the structure, synthesis, isolation and structural activity relationship with the pharmacological activity.

Medicinal chemistry

Medicinal chemistry and bioorganic chemistry is concerned with the design, synthesis and analysis of the relationship between molecular structure and biological activity for compounds that can be used for the care or treatment of disease[2-8].

In medicinal chemistry, the chemist attempts to design and synthesis a medicine or pharmaceutical agent which will benefit humanity. Such a compound could be called as a 'drug'.

Medicinal chemistry is a part of pharmaceutical chemistry. Medicinal chemistry is discipline at the intersection of chemistry and pharmacology involved with designing, synthesizing and developing pharmaceutical drugs. Medicinal

chemistry involves the identification, synthesis and development of new chemical entities suitable for therapeutic use. It also includes the study of existing drugs, their biological properties and their quantitative structure activity relationship (QSAR).

Medicinal chemistry is the application of chemical research techniques to the synthesis of pharmaceuticals. During the early stages of medicinal chemistry development, scientist were primarily concern with the isolation of the medicinal agents founds in plants. Today, scientists in this field are also equally concerned with creation of new synthetic drug compounds. Medicinal chemistry almost always geared towards drug discovery and development.

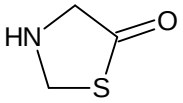
The first step is pharmaceutical focused on quality aspects of medicines and aims to assure fitness for the purpose of medicinal products. Medicinal chemistry is a highly interdisciplinary science combining organic chemistry with biochemistry, computational chemistry, pharmacology, pharmacognosy, molecular biology, statistics and physical chemistry.The second step of drug discovery involves the synthetic modification of the hits in order to improve the biological properties of the compound pharmacophore.

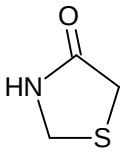
Heterocyclic chemistry[9-15] is the chemistry branch dealing exclusively with synthesis, properties and application of heterocyclic. Heterocyclic compound is an organic compound that contains a ring structure containing atom in addition to carbon, such as sulfur, oxygen or nitrogen as part of the ring. They may be either simple aromatic or non-aromatic rings. Some heterocyclic compounds are known as carcinogens. Researchers have show that heterocyclic amines are the Carcinogenic chemicals.

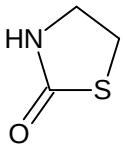
A heterocyclic compound is one which possesses a cyclic structure with at least two different kinds of hetero atoms in the ring. Nitrogen, oxygen and sulphur are most common hetero atoms. Heterocyclic compounds are very widely distributed in nature and are essential to life in various ways.

1.2. THIAZOLIDINONE

Thiazolidin-4-one[16-19] occurs as yellow crystal and odorless. It is soluble in water, ethanol and solvent ether. Tetra hydro derivative of thiazole ring is known as thiazolidine[25,26].







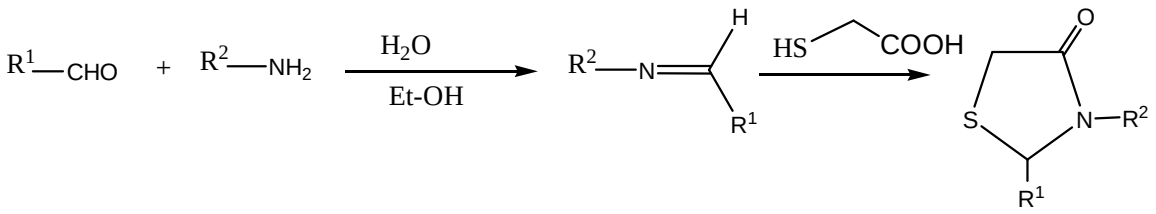
Thiazolidin-5-one Thiazolidin-4-one Thiazolidin-2-one

Thiazolidin-4-one and its derivatives have high pharmacological relevance since they are available in both natural products and Pharmaceutical compounds[20-25].

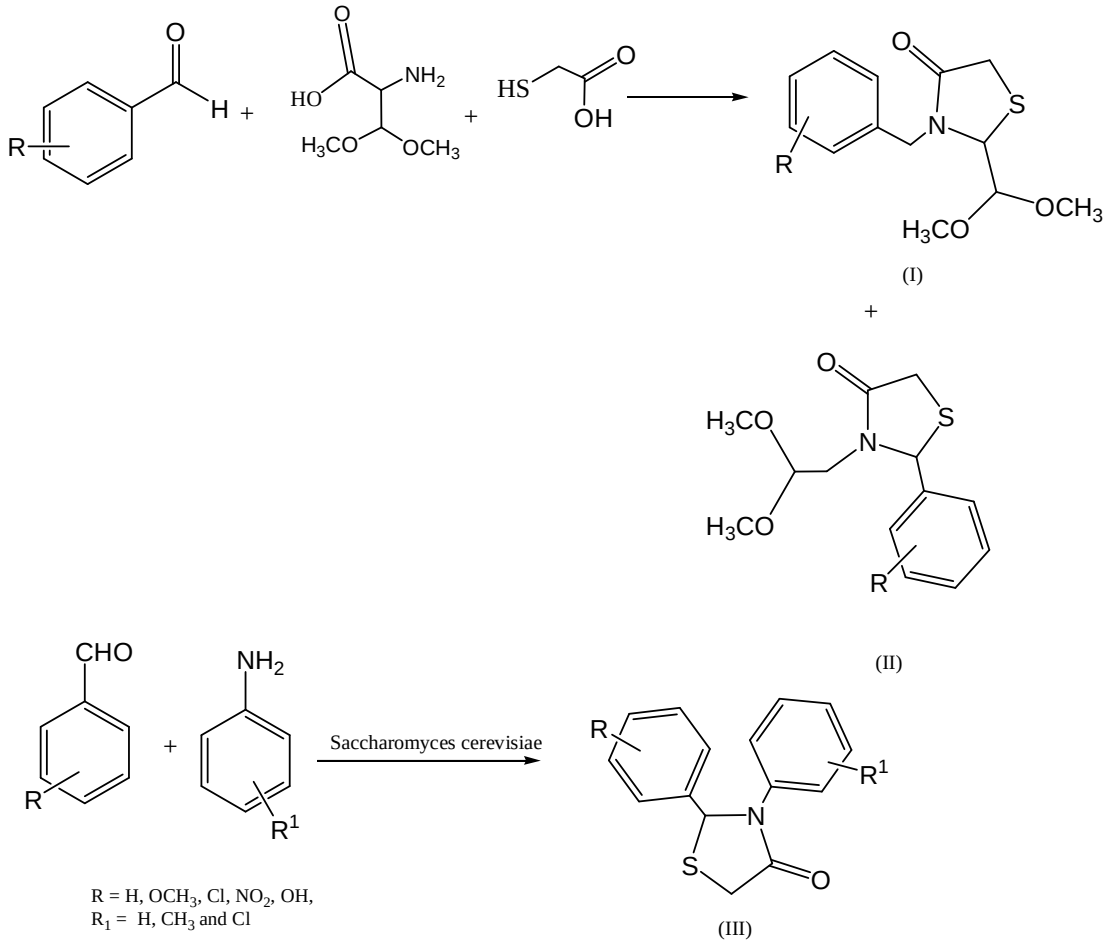
Method of preparation

The number of methods for the synthesis of thiazolidinones is widely reported in the literature. The main synthetic routes to thiazolidin-4-ones comprising three components such as an amine, a carbonyl group and mercapto acid. The classical method of synthesis reported may be either a one-pot three-component condensation method or a two-step process. The reaction starts by formation of an imine which undergoes attack by sulfur nucleophile, followed by intramolecular cyclization to eliminate water[27].

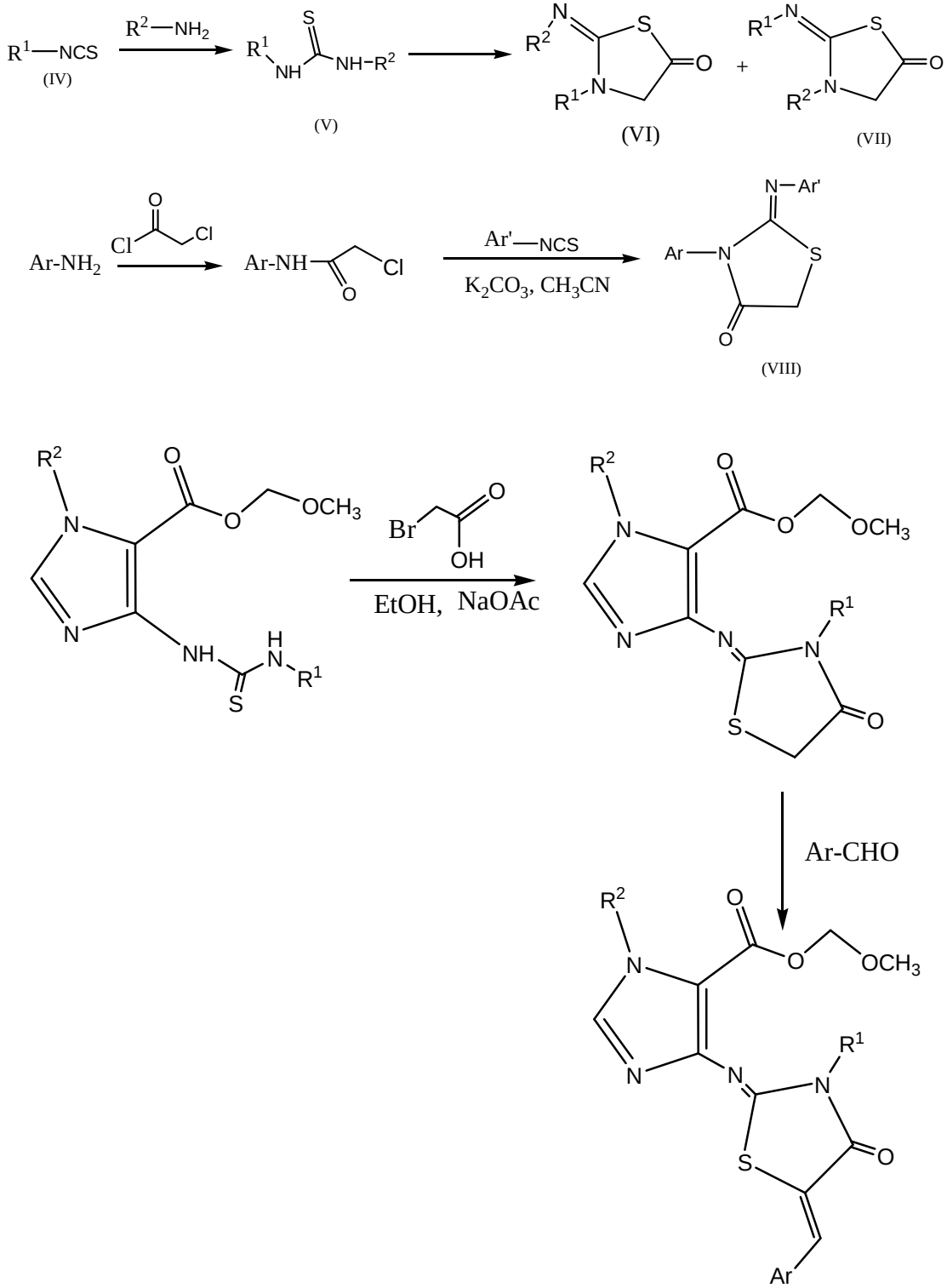
Kozlov co-workers[33] reported a one-step cyclization reaction where in the reaction of ethyl 5-phenyl thioureido-3-imidazole-4-carboxylate with bromoacetic acid gives an imidazolylimino thiazolidin-4-one. This cyclization reaction starts by one of the nitrogen atom of nucleophilic centers in 5-thioureido-3-imidazole-4-carboxylic acid derivative yields the desired thiazolidin-4-ones[28-34].



Further, new synthetic route[35] for the preparation of 2-isopropyl-3-benzyl-1,3-thiazolidin-4-ones and 2-phenyl-3-isobutyl-1,3-thiazolidin-4-ones by using 1:1:3 ratio of valine, aldehyde and mercaptoacetic acid was reported by Cunico[36] *et al.*,., and suggested that the introduction of strong withdrawing group such as NO_2 present in benzaldehyde favored the synthesis of hetero-cycle (**I**) in good yields, whereas the methoxy and fluoro groups produces the type (**II**) thiazolidin-4-ones. In this connection a solvent-free synthesis of five-membered heterocyclic thiazolidin-4-ones from phenyl hydrazine and 2,4-DNP as an amino moiety[37]. Another method of preparation of 2,3-diaryl-thiazolidin-4-ones (**III**) was established, where *saccharomyces cerevisiae* enzyme also called as baker's yeast comprising lipase was used as a catalyst in this reaction and accelerated the formation of imines as well as cyclo-condensation reaction of aryl aldehydes, amines with thioglycolic acid.



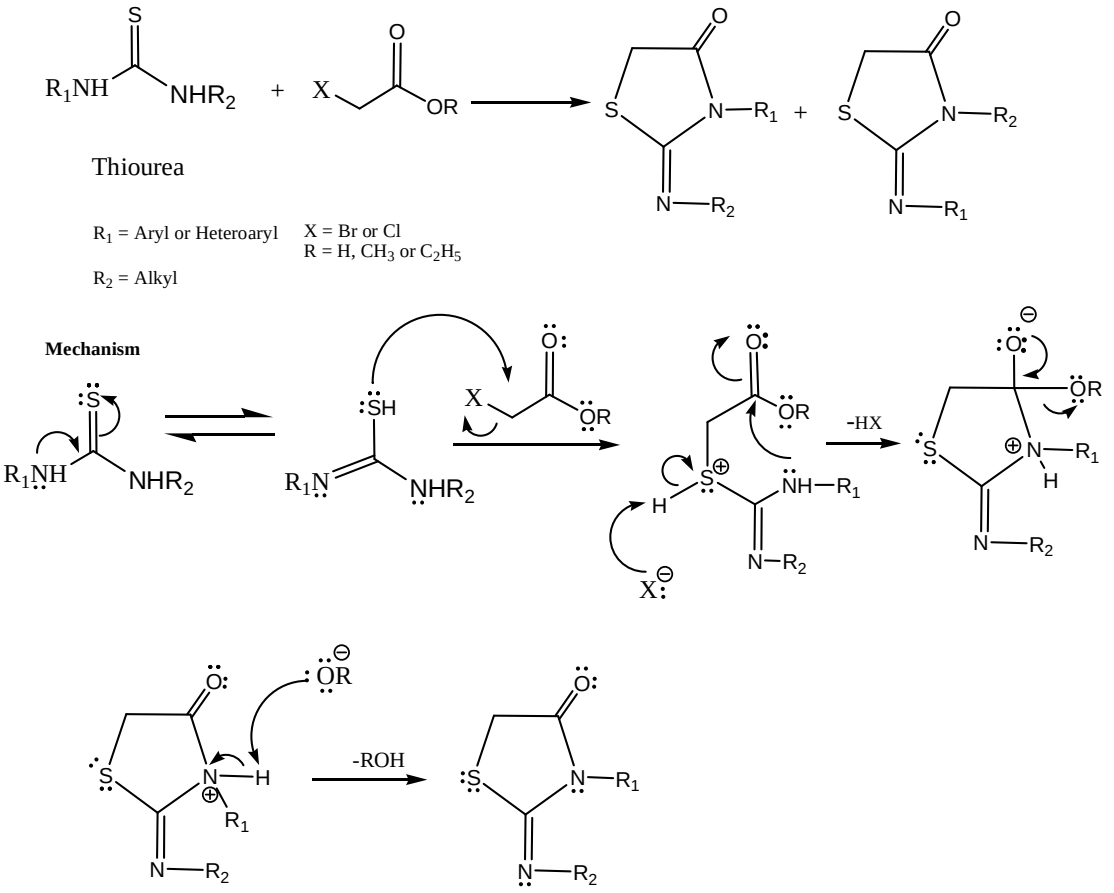
Further, the reaction of alkyl or aryl isothiocyanate (**IV**) with a primary amine furnished the corresponding thiourea derivative (**V**), which directly undergoes cyclization reaction by treating with halo acetic acid to yield two isomers of 2-imino-thiazolidin-4-ones[38](**VI, VII)**. In addition, coupling reaction between α-chloro amide derivatives with an isothiocyanate in the presence of a mild base such as K_2CO_3 afforded the iminothiazolidin-4-one derivatives[39] (**VIII**).



Mechanism of reaction for the preparation of thiazolidinones

The reaction between substituted thiourea with acid to haloacetic acid produces 2-imino thiazolidin-4-ones. These reactions occur in polar solvents such as ethyl alcohol

under reflux and in the presence sodium acetate or pyridine[40]. Substituted thiourea can be procured by a reaction with primary amines. Thiourea undergoes asymmetric reactions and form two regioisomers, where the regioselectivity is controlled by electronic factors, especially the combination of electron-withdrawing substituent (aryl or heteroaryl) with nitrogen imino group[41].



Properties of thiazolidin-4-ones

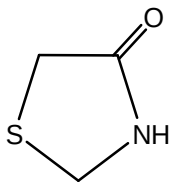
The thiazolidin-4- ones are generally solid forms, often melting with decomposition but the attachment of alkyl group with the nitrogen minimizes the melting point. The aryl or higher alkyl substituent's of thiazolidin-4-one slightly soluble in water.

Chemical properties of thiazolidin-4-ones

The structure of thiazolidin-4-ones exists in the literatures[42]. Thiazolidin-4-ones are the derivatives of thiazolidine with C=O group at fourth position[43]. Substitution of various groups at 2^{nd}, 4^{th} and 5^{th} position is possible. A different optical isomeric form of thiazolidinone is reported in the references[44] and number of regioselective isomers has been reported[45,46]. The C=O group of thiazolidin-4-one is highly inert nature. But in few cases thiazolidin-4-one on reaction with Lawesson's reagent gives corresponding thiazolidin-4-ones[47]. Tautomer of 2-imino thiazolidine-4-one found to exhibit some chemical interest.

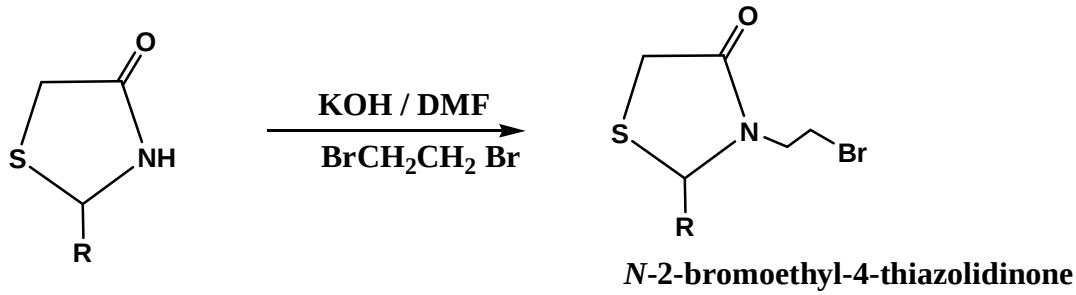
Several methods are available in order to synthesis a thiazolidin-4-ones in the literatures[47] which involve conventional, microwave irradiation method and combinatorial synthesis. The reaction between NH_2 with CS_2 in the presence of alkali which then reacts with haloalkanoic acid in the presence of Na_2CO_3 yields thiazolidin-4-ones.

Among the various reactions involving the thiazolidin-4-one ring, reactions occurring at first position (sulfur) in the oxidation reaction, third position (nitrogen) in N–alkylation reaction and mannich reaction, fourth position (C=O) in thionation reaction via Lawesson's reagent[49] and fifth position (CH_2) in condensation reaction with aldehydes and ketones or diazonium salts is processed. Here by all the above reactions are disussed in detail.



***N*–alkylation reaction**

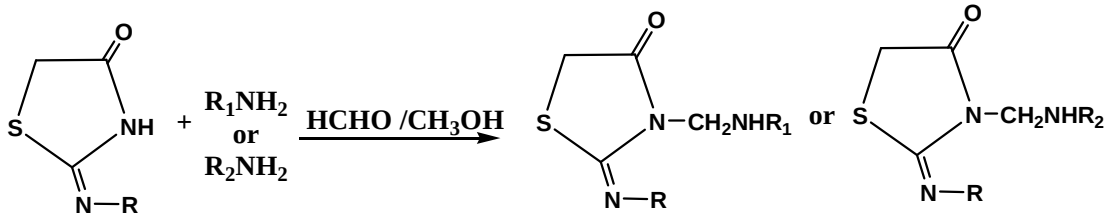
Jelte.N and co-workers[50] found that thiazolidin-4-ones substituted in the second position with alkyl or alkoxy groups undergo an *N*-alkylation reaction. In this method, equivalent amount of potassium hydroxide was used with thiazolidin-4-ones in anhydrous DMF which promotes the formation of amide anion through the abstraction of hydrogen at N-3 position and subsequent attack of this anion with 1, 2-dibromo ethane at room temperature. The use of potassium hydroxide is essential for the formation of amide anion, since thiazolidin-4-one unsubstituted in third position are weak acids.



***N*-2-bromoethyl-4-thiazolidinone**

Mannich reaction

Mannich reactions are generally occur between 2-imino thiazolidin-4-ones and NH_2 or NH in presence of formaldehyde or paraformaldehyde in methyl alcohol to produce 2-imino-3-(substituted amino methyl) thiazolidin-4-one[51].

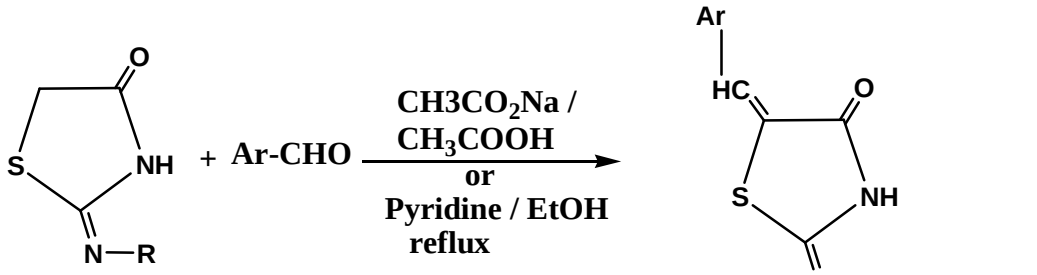


2-imino-4-thiazolidinone

2-imino-3-aminoalkyl /aryl- 4-thiazolidinone

Condensation reaction with aldehydes

The CH_2 group at fifth position of thiazolidin-4-one ring due to its acidity it undergoes condensation reaction with aldehydes or ketones in knoevenagel reaction[52]. In this reaction, formation of an enolate intermediate is stabilized, which is more dependent on the electron attractive effect of the C=O group adjacent to the CH_2 group and the presence of electron-attractive group at second position of thiazolidin-4-one ring. The condensation reaction typically occurs in presence of glacial acetic acid and sodium acetate where sodium acetate functions as both alkali and as well as a dehydrating agent in piperidine solution or ethanol.



2-imino-4-thiazolidinone

2-imino-5-arylidene-4-thiazolidinone

1.3 CANCER AND ANTI CANCERAGENTS

Today, the Greek term carcinoma is the medical term for a malignant tumor derived from epithelial cells. It is cells us who translated carcinos in to the Latin cancer, also meaning crab. Galen used “oncos” to describe all tumors, the root for the modern word oncology[53].

Cancer is an important public health on concern and in developed countries it represents the second leading cause of death, after cardiovascular disease. The resistance to chemotherapeutic anti-tumoragents by cancer cells could be minimized using a combination of drugs with different and complementary mechanism of action. Therefore,

there is a need to discover and develop useful new lead compounds of simple structure, exhibiting optimal *invivo* anti tumor potency and new mechanism of action.

Cancer[54] is a disease in which a group of cells divides abnormally without any control, even destroy other tissues. These cells spread all over the body through the blood and lymph, giving rise to satellite lesions elsewhere and then eventually leading to death.

Cancer is one of the most wide spread and feared diseases in the western world today feared largely because it is known to be difficult to cure. The main reason for this difficulty is that cancer results from the uncontrolled multiplication of subtly modified normal human cells.

One of the main method so far modern cancer treatments is drug therapy (chemotherapy). Cancer is a major disease about one in four people will getting some form during their lifetime, and at the present time about one in five of all death are due to cancer.

Currently the rare three major ways of treating cancer:

- Radiation therapy
- Surgery
- Cytotoxic drugs.

Cancer arises from the mutation of a normal gene. Mutated genes that cause cancer are called **oncogenes**. A factor which brings about a mutation is called a mutagen. Any agent that causes a cancer is called a **carcinogen** and is described as **carcinogenic**[55].

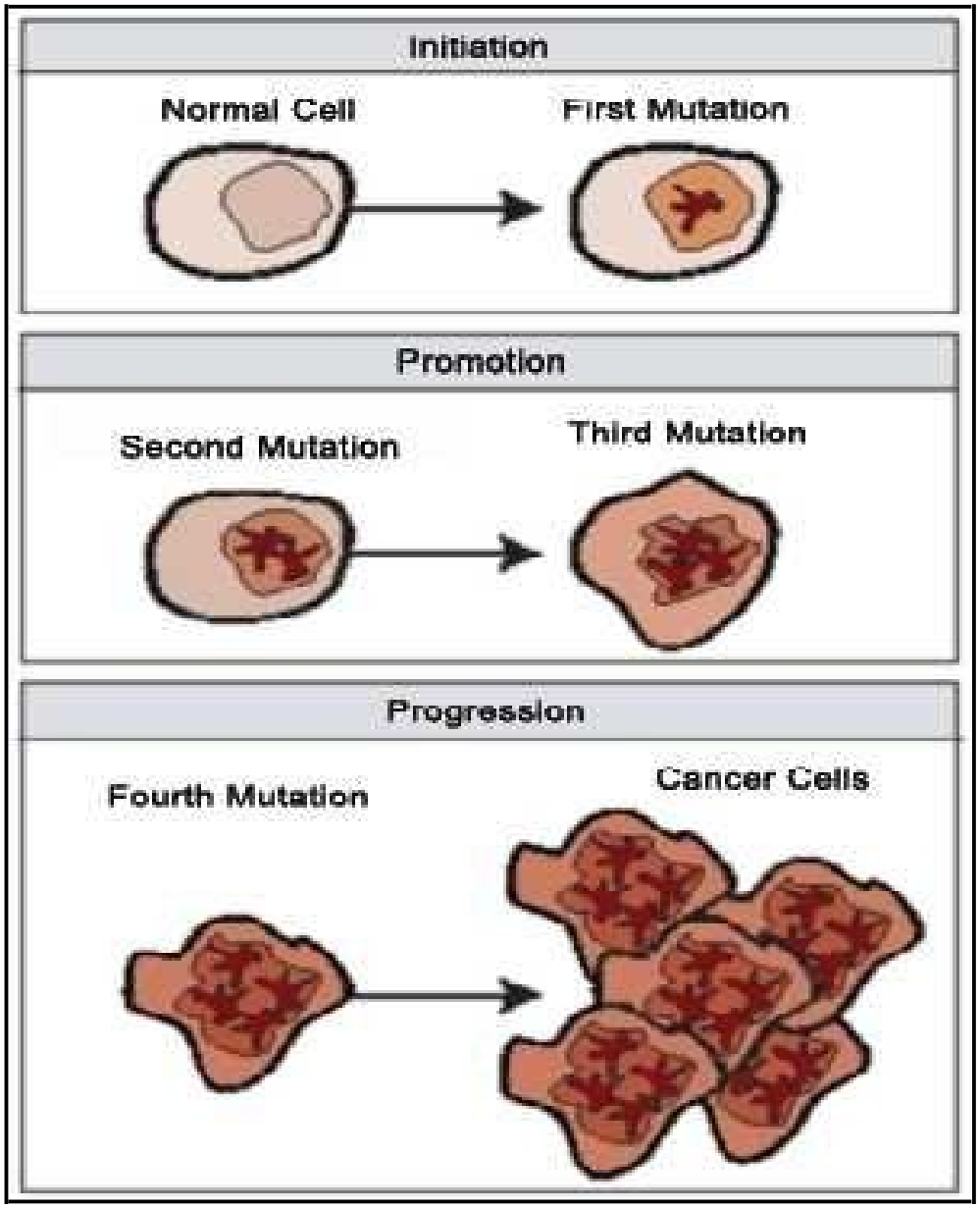


Fig.No.1 Types of cancer scell division

Types of tumor

1. Benign tumours (do not spread from their site of origin, but can crowd out (squash) surrounding cells e.g. brain tumor

2. Malignant tumours (can spread from the original site and causes secondary tumours. This is called metastasis. They interfere with neighboring cells and can block blood vessels, the gut, glands, lungs etc.)

The Cell Cycle

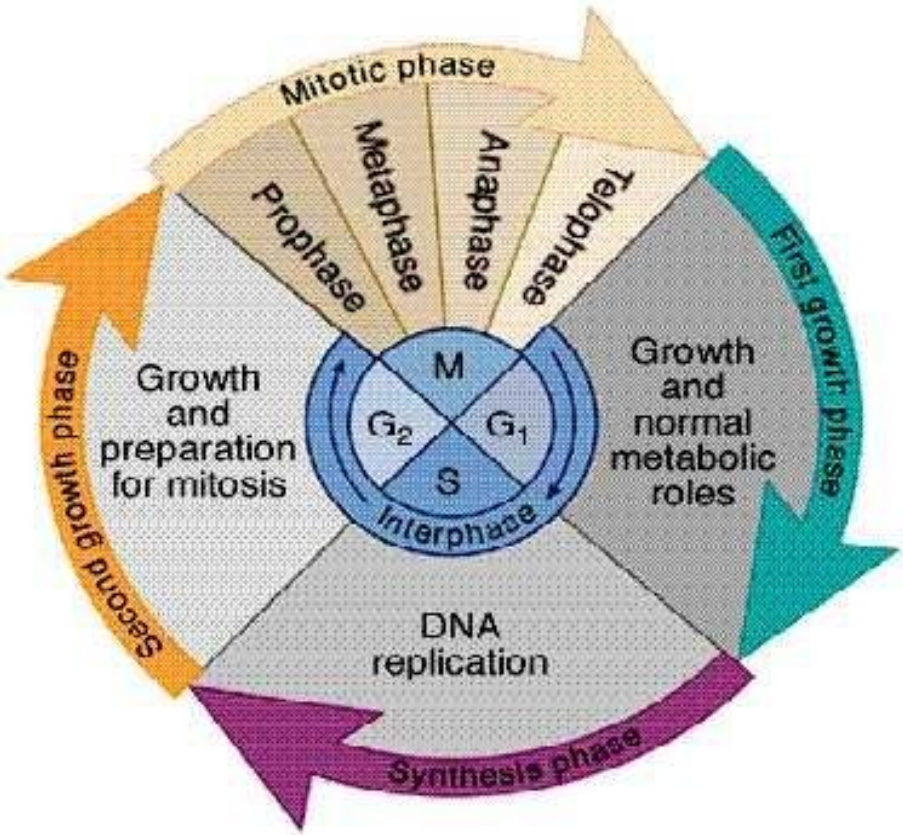


Fig.No.2 Phases of Cell cycle

- The cell cycle consists of four stages G1, S, G2 and M.
- G1 and G2 are 'gap' phases in which the cell grows and prepares to divide.
- S is the synthesis phase in which the chromosomes (DNA) are copied (replicated).
- M is the mitotic phase in which the cell physically divides in to two daughter cells.
- Most cells are NOT actively dividing. These cells are in a resting state(G).

Mitosis (M phase)

- Mitosis in normal cells produces two cells with identical genetic content.

Mitosis has four sub-phases.

- Prophase -Chromosomes condense, then clear membrane breaks down and spindle fibres form.
- Metaphase-The replicated chromosomes line up in the middle of the cell.
- Anaphase-Chromosomes separate and the cell become elongated with distinct ends (poles).
- Telophase - Nuclear envelopes reform at the two poles and new cell membranes are formed to create two independent cells.
- Cytotoxicity is the cell killing property of a chemical compounds. Cell death can occur by either of two distant mechanism, necrosis or apoptosis.

Necrosis is physical or chemical damage, where apoptosis is the physiological process by which unwanted cells are eliminated during development and other normal biological processes.

Types of cancer

Lung Cancer	Lung
Breast Cancer	Breast
Cervical Cancer	Cervical
Colon Cancer	Colon
Leukemia	Blood
Testicular Cancer	Testis
Brain Cancer	Brain
Kidney Cancer	Kidney
Thyroid Cancer	Thyroid Gland
Liver Cancer	Liver
Bone Cancer	Bone marrow

Table No.1 Types of Cancer

Causes of cancer

- DNA Mutation
    1. Radiation – other environmental (tobacco, alcohol, radon, asbestos, chemicals etc).
    2. Random somatic mutations
    3. Inherited germ line mutations
- Genetic predisposition –
    1. Rb, p53, APC, CDKN2A, BRCA1, BRACA
- Infectious agents

1. Viral

A. HPV (Human papilloma virus) – cervical cancer

B. Hepatitis – liver cancer

2. Bacterial

A. *H. pylori*– stomach cancer

Diagnosis of cancer

- Biopsy of the tumor
- Blood tests (which look for chemicals such as tumor makers)
- Bone marrow biopsy (for lymphoma or leukemia)
- Chest x-ray
- Complete blood count
- CT scan & MRI scan

Treatment of Cancer Traditional treatment

1. Surgery: it is the first treatment which is used to removed solid tumors, and for early stage cancer and benign tumors.

2. Radiation: it kills the cancer cells with high energy rays targeted to the tumor. It acts by damaging DNA and preventing its replication.

Newer treatment

1. Hormone therapy: by using Hormones and anti – Hormone.

2. Chemotherapy: Chemotherapy means treatment with anticancer drugs and they are given to destroy or control cancer cells.

1.4 CERVICAL CANCER

The American Cancer Society's[56-60] most recent estimates for cervical cancer in the United States are for 2011:

- About 12,710 new cases of invasive cervical cancer will be diagnosed per year.
- About 4,290 women will die from cervical cancer per year

Cervical cancer is one of the most common types of cancer and a majority mortality factor of women worldwide.

The cervix is the lower part of the uterus (womb). The part of the cervix closest to the body the uterus is called the endocervix. The part next to the vagina is the exocervix. The two main types of cells covering the cervix are squamous cells (on the endocervix). The place where these two cell types meet is called the transformation zone. Most cervical cancers start in the transformation zone.

Normally, cervical cells grow in an orderly fashion. However, when controls of that grow this lost, cells divide too frequently and too fast. Nearly all cervical cancers arise of the inner of the cervix.

There are several types of cervical cancer:

Squamous cell carcinoma[61] (SCC) is the most common type of cervical cancer, accounting for 85% to 90% of all cases. It develops from the cells that line the inner part of the cervix, called the squamous cells.

Adenocarcinoma[62] develops from the column shaped cells that line the mucous producing glands of the cervix. In rare instances, adenocarcinoma accounts for about 10% of all cervical cancers.

Mixed carcinomas (adenosquamouscarcinomas)[63] combine features of both squamous cell carcinoma and adenocarcinoma.

Treatment of Cervical Cancer

- Surgery
- Pre invasive cervical cancer
- Cryosurgery
- Laser surgery
- Invasive cervical cancer

1. Simple hysterectomy– removal of the body of the uterus and cervix 2. Radical hysterectomy and pelvic lymph node dissection Removal of entire uterus, surrounding tissue, upper part of the vagina and lymph nodes from the cervix.

- Radiation
- Chemotherapy

The drugs used to combat cancer belong to one of the two broad categories. The first is cytotoxic drugs (cell killing) and the second is cytostatic drugs (cell stabilizing). Both the categories lead to a reduction in the size of tumor because cancer cells (for various reasons) have such a high mortality rate that simply preventing them from dividing will lead to a reduction in the population.

The majority of drugs used for treatment of cancer today are cytotoxic (cell killing) drugs that work by interfering in someway with the operation of the cell's DNA. Cytotoxic drugs have the potential to be very harmful to the body unless they are very specific to cancer cells something difficult to achieve because the modifications that change a healthy cell in to a cancerous one are very subtle. A major challenge is to design new drugs that will be more selective for cancer cells, and thus have lesser side effects.The development of a new pharmaceutical is a complex process, but can be broken down to three main steps:

- Discovery of a new potentially use full molecule.
- Appropriate molecular modification to produce a molecule with the best combination of properties.
- Development of this molecule in to a safe and affordable drug.

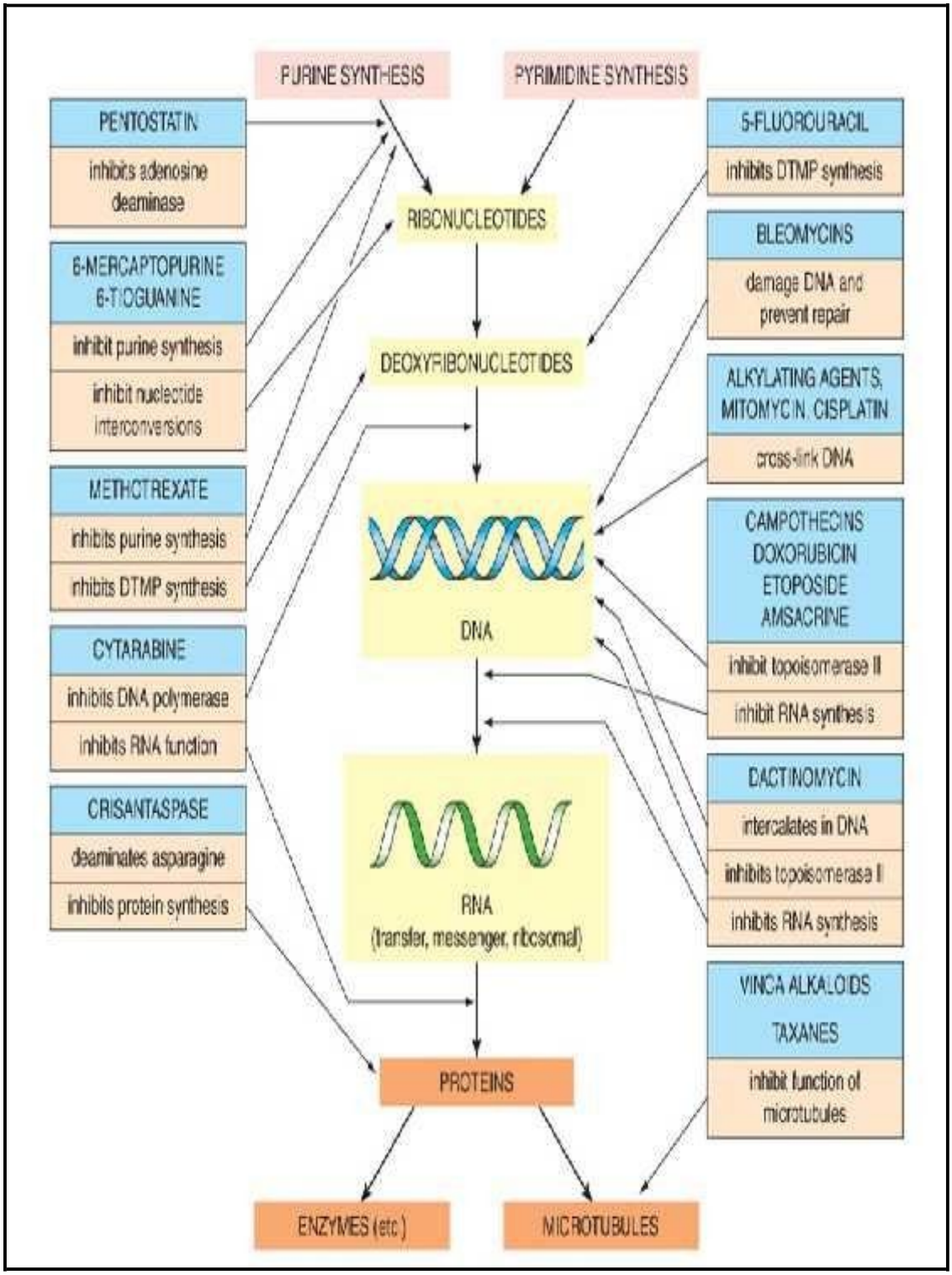


Fig.No.4 MOA of Cytotoxic drugs

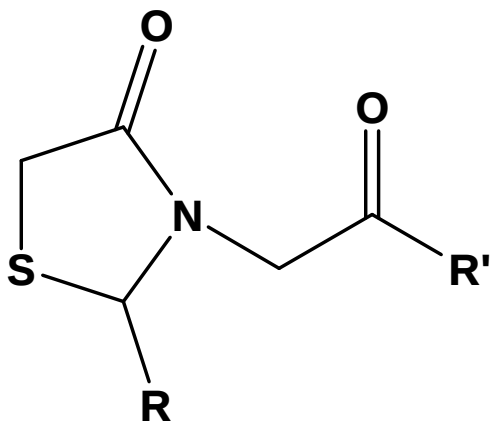
2. LITERATURE REVIEW

Various thiazolidinone derivatives have been developed by structural modifications in order to enhance the biological properties such as anticancer, anticonvulsant, CNS depressant, analgesic, anti-inflammatory, etc. Here in a detailed literature survey is described for thiazolidinone derivatives.

2.1 ANTICANCER ACTIVITY

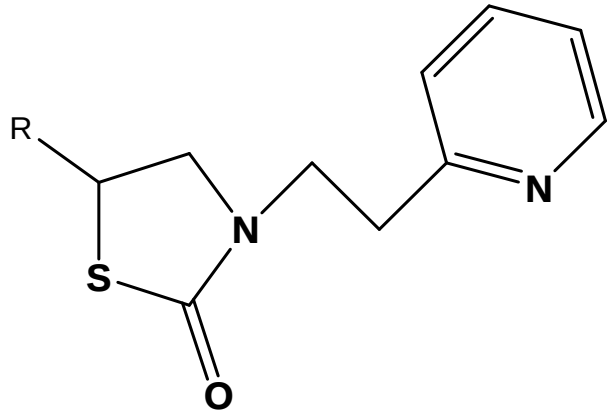
Monforte and co-workers[64] in the year 1988 reported the antitumor activity of series of 2-alkyl-[2-(1, 3, 4-thiadiazolyl)]-4-thiazolidinones. These compounds were tested against the leukemic 388 tumor system. All the compounds were found to exhibited significant antitumor activity.

Duane D Miller and co-workers[65] in the year 2004 reported the synthesis, SAR and antiproliferative activity of 2-aryl-4-oxo-thiazolidin-3-yl-amides **(1)** for prostate cancer. From this study, three potent compounds have been detected, which were effective in killing prostate cancer cells with improved selectivity.



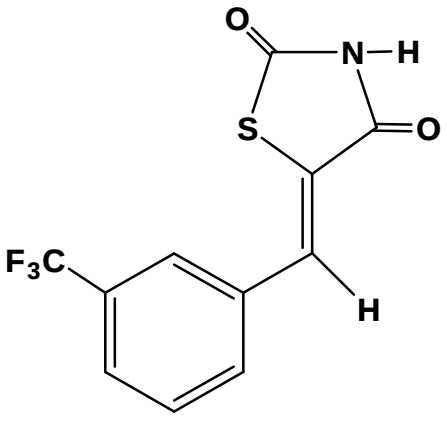
(1)

Roman Lesyk and co-workers[66] in the same year have reported some novel 4-thiazolidones **(2)** derivatives and studied their anti-diabetic (insulin-sensitizing), aldose reductase, thyromimetic, antimicrobial, antiviral, anti-ischemic, cardiovascular and anticancer activity.



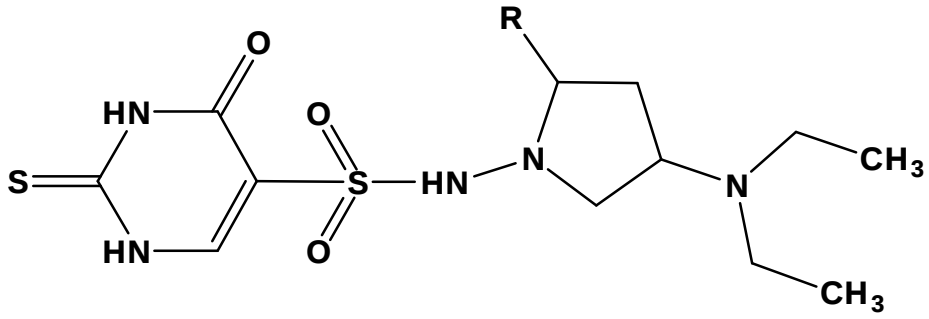
(2)

In the year 2005, Stefania Carotti and co-workers[67] reported *in-vitro* anti-proliferative activity of 4-thiazolidinones against human colon cancer cell lines. The 2-phenyl imino and 2,4-thiazolidinone **(3)** derivatives were found to be the most active compounds. 2-Phenyl imino derivative inhibits the HT 29 cell line by a high COX-2 expression and 2,4-thiazolidinones inhibits all cell lines.



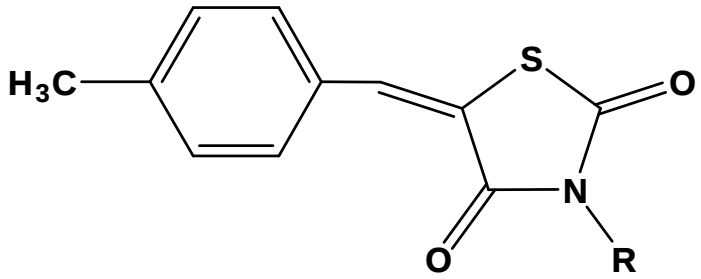
(3)

AmanySayed Maghraby and co-workers[68] in the year 2005 reported the synthesis of series of new 4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine (**4)** derivatives incorporated thiazolidinone moiety. The synthesized compounds were tested for possible serine prostate and cercarialelastase inhibitory effects with a possible prospective to block penetration of schistosomamansonicercariae in to the skin.



(4)

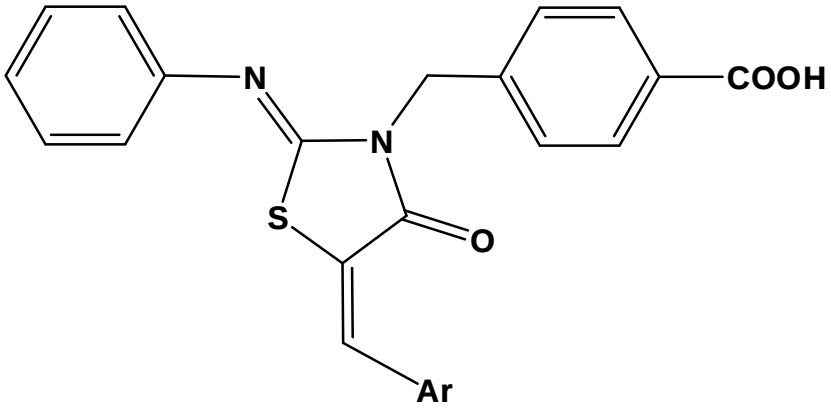
Benaka Prasad and co-workers[69] in the year 2008 synthesized a series of novel 5-(4-methyl benzylidene)-thiazolidine-2,4-dione **(5)** derivatives with different substituted aromatic sulfonyl chlorides and alkyl halides. The synthesized compounds were evaluated for their cell antiproliferative activity by MTT assay. The nitro group in the 4th position on aryl ring plays a dominant role and was responsible for the antiproliferative activity.



(5)

Shuhong Wu and co-workers[70] in the year 2008 reported the synthesis of pharmacophore of thiazolidinone derivatives. The synthesized compounds were evaluated for their structure activity relationship, cytoselective toxicity and anti-cancer activity.

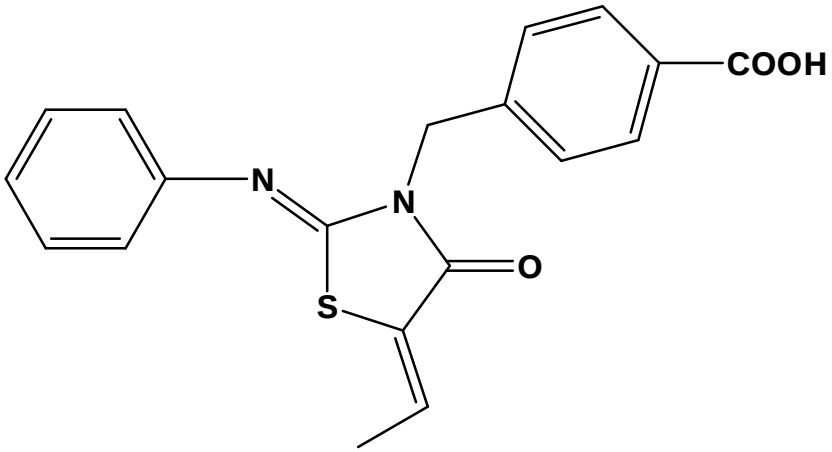
In the year 2009 Rosanna Maccari and co-workers[71] synthesized 4-(5-arylidene-4-oxo-2-phenylimino thiazolidin-3yl)-methyl benzoic acids **(6)** and screened their inhibitory activity against human PTP1b and LMW-PTP enzymes. Among the evaluated compounds, the 5-arylidene substituted moiety proved the potency.



(6)

In the same year, Zimenkovsky and co-workers[72] have synthesized a novel nonfused bicyclic thiazolidinones. These compounds were screened for their anticancer activity. Among the tested compounds, the compound 2-(4-oxo-3-furyl methyl-4-oxothiazolidin-5-yl-*N*-4-chlorophenyl) acetamide was found to be more potent anticancer agent than the standard compound.

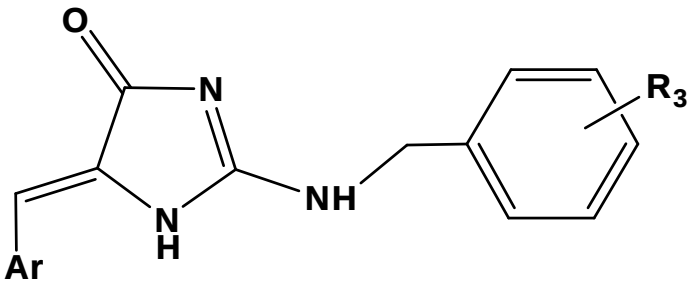
HavrylyukDmytro and co-workers[73] in the year 2010 reported the synthesis and anticancer activity evaluation of 4-thiazolidinones **(7)** containing benzothiazole moiety. These compounds were screened for *in-vitro* anticancer activity. The activity data exhibits that all compounds were found to show potent anticancer activity.



(7)

Kaminskyy DV and co-workers[74] in the year 2010 described the structure–anticancer activity relationships among 4-thiazolidinone-3-carboxylic acids derivatives.

In the year 2010, IvannaSubtelna and co-workers[75] synthesized the 5-arylidene-2-amino-4-thiazolones **(8)** and evaluated their anticancer activity. The synthesized compounds were found to possess a good anticancer activity. Among the tested one, the compounds 5-(4-chlorobenzylidene)-2-(4- hydroxyl phenyl amino) thiazol-4-one and 5-(2-chloro-3-(4-nitrophenyl)-2-propenylidene)-2-(3-hydroxyphenylamino) thiazol-4-one were found to possess high effect on all leukemia cell lines.



(8)

In the year 2011 Maity TK and co-workers[76] reported the synthesis, characterization and antiproliferative activity of 2-(substituted phenyl)-5-methyl-3-pyridin-4yl-1,3-

thiazolidinones. These compounds were evaluated for *in-vitro* cytotoxicity against lymphoma cancer cell lines at varies concentrations. Among the tested compounds, two compounds showed highest cytotoxic activity against L929 cell lines.

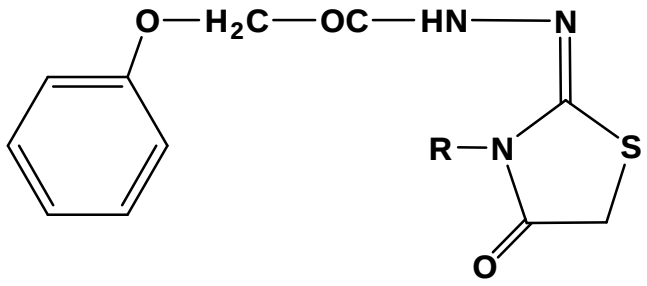
A series of regioselective 3-thiazolidine acetic acid derivatives were synthesized by Zhengming Li and co-workers[77] in the year 2011. These compounds were evaluated for anti-tumor activity. The results of bioactivity data showed that modification at the C-H of amino acid, N-(per-*o*-acetyl glycosyl amino) thioxo methyl) ethyl ester results in great influence on anti-tumor activity.

Ping Gong and co-workers[78] in the year 2012 reported the design and synthesis of 2-iminothiazolidin-4-one moiety-containing compounds as potent antiproliferative agents. The Pharmacological data indicated that most of the compounds possessed moderate activity, some showed remarkable activity.

2.2 ANTIDIABETIC ACTIVITY

Pattan and co-workers[79] in the year 2005 reported the synthesis and anti-diabetic activity of 2-amino [5 (- 4 - sulfonylbenzylidine) - 2,4-thiazolidindione] -7- chloro – 6 - flurobenzothiazole. The synthesized compounds were found to possess potent anti-diabetic activity.

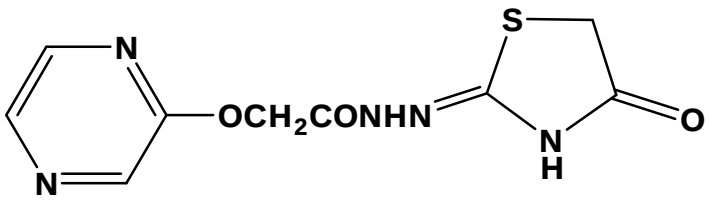
In the year 2009, Firake BM and co-workers[80] reported the synthesis of series of *N*-ary/alkyl substituted pyridine thiazolidinones**(9)**. These compounds were screened for their antidiabetic acitivity on wistar-strain rats and acute toxicity. All the tested compounds were found to possess good antidiabetic activity.



(9)

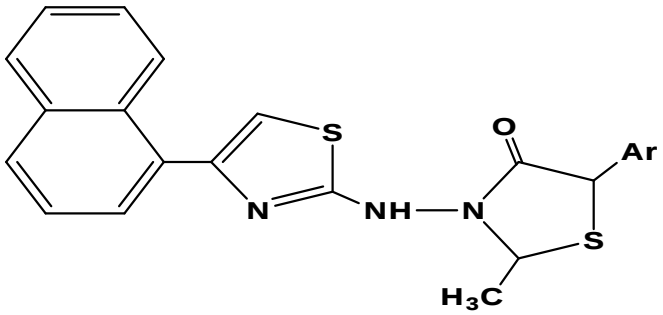
Suroor Ahmad Khan and co-workers[81] in the same year have prepared a series of 2-substituted phenyl-3-(1-naphthyl)-1,3-thiazolyl-amino-4-oxo thiazolidin acetic acid derivatives and evaluated their anti-hyperglycemic activity. The bioactivity results revealed that all compounds possess more potent antihyperglycemic activity.

In the year 2010, VipanKamboj and co-workers[82] synthesized a series of 3-(4-alkyl/arylsubstituted)-4-oxo-1,3-thiazolidin-2-ylidene acetohydrazide**(10)**. All the compounds were screened for their antidiabetic activity. Among the tested compounds, the compound 3-phenyl substituted-4–oxo-1,3-thiazolidin-2-ylidene acetohydrazide possess high activity with reduced toxicity.



(10)

Synthesis of 5-substituted-1,3-thiazolidin-4-ones **(11)** as anti-hyperglycemic activity was reported by BirendraSrivastava and co-workers[83] in the year 2010. These compounds were found to possess good anti-hyperglycemic activity.

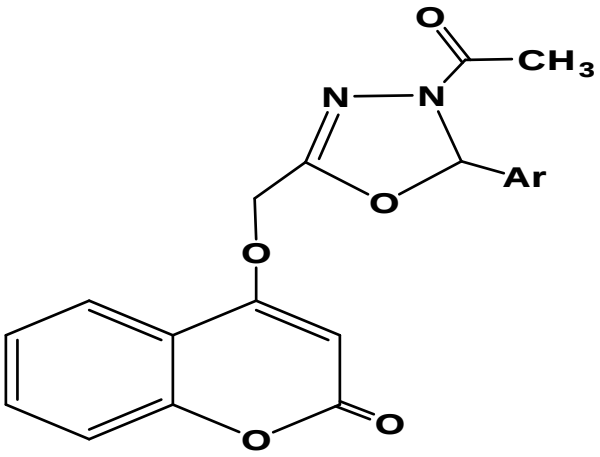


(11)

DeepthiKini and co-workers[84] in the year 2011 reported the synthesis of new series of 3-(5-methyl-2-aryl-3-thiazolylamino)-4- thiazolidinone coumarin derivatives. The prepared compounds have been evaluated for their oral hypoglycemic activity. Among the tested compounds, the compound 3-(5–methyl–3-(4–nitrophenyl)–3-thiazolylamino-4-thiazolidinone coumarin exhibited high profile of activity when compared to standard.

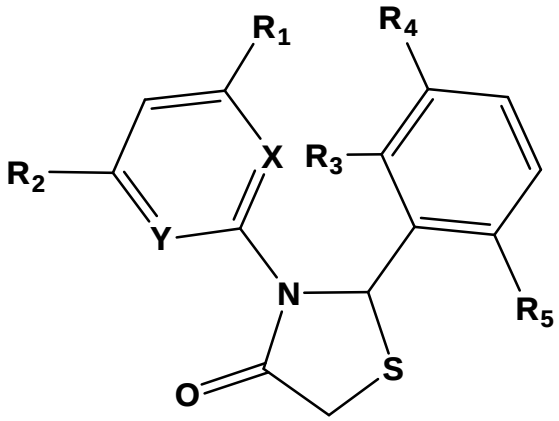
2.3 ANTI-VIRAL ACTIVITY

FaridBadria and co-workers[85] in the year 2003 synthesized a new thiazolidinone and oxadiazoline coumarin**(12)** derivatives and investigated their antiviral activity, cytotoxicity and SAR studies. All compounds were found to exhibits high antiviral profiles.



(12)

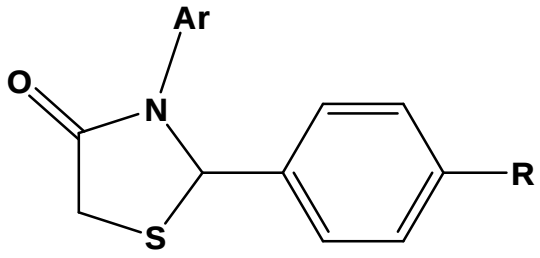
Synthesis of benzimidazole and thiazolidinone derivative **(13)** as HIV-1 RT inhibitors by microwave irradiation technique was reported by Anna Maria Monforte *et al.,*[86] in the year 2004. Among the evaluated compounds the compound 2-(2,6-difluorophenyl)-3-(3-methoxyphenyl)-1,3-thiazolidin-4-one emerged as potent HIV-1 with marked RT inhibitory affects.



(13)

Zappala and co-workers[87] in the year 2004 synthesized 1,3-thiazolidinones with dihalogen and pyrimidine substitution. The prepared compounds were screened for their HIV-1 reverse transcriptase enzyme inhibition studies. From the activity data it was found that all the compounds were found to possess good HIV-1 activity.

In the year 2005, Dharmarajan Sriram and co-workers[88] reported the synthesis and anti-YFV activity of 2, 3-diaryl-1,3-thiazolidin-4-ones **(14)** by microwave-assisted reaction. The synthesized compounds were evaluated for their inhibitory effects on the replication of YFV in green monkey kidney (Vero) cells (ATCC CCL81), by means of a cytopathic effect reduction assay.



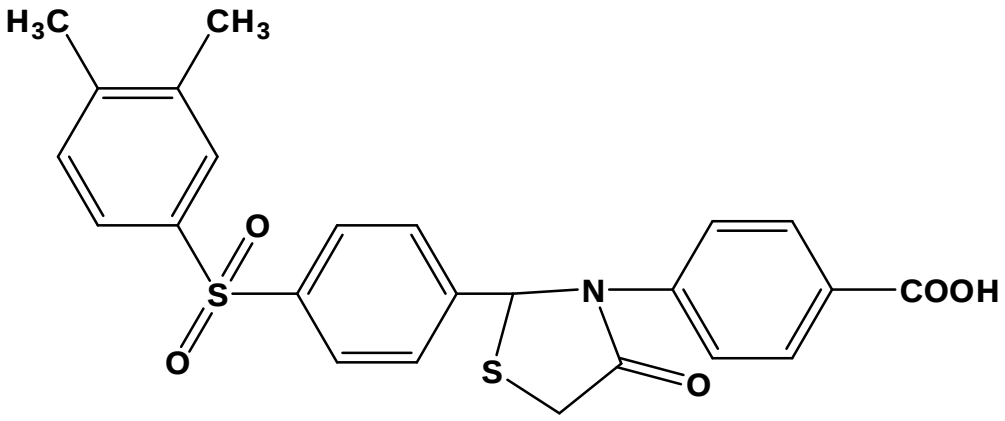
(14)

Ravindra K Rawal and coworker[89] in the year 2007 reported molecular docking studies of 4-thiazolidinones as HIV-1 RT inhibitors. The docking studies provided an insight into the pharmacophoric structural requirements for the HIV-1 RT inhibitory activity of this class of molecules.

In the year 2011, Ravichandran Veerasamy and co-workers[90] has reported the design, synthesis and biological evaluation of thiazolidinone derivatives as potent anti-viral agents. All the compounds possessed high degree of antiviral potential.

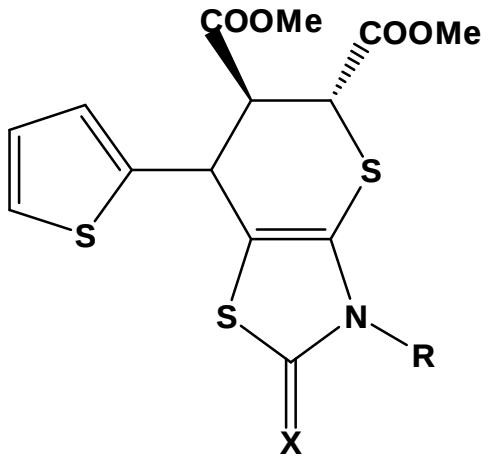
2.4 ANTIMYCOBACTERIAL AND ANTIFUNGAL ACTIVITY

Evelin Boshra and co-workers[91] in the year 1989 reported some new heterocyclic thiazolidines**(15)** with acaricidal, insecticidal and bactericidal activity. The reported compounds were found to possess a good bactericidal and inseticidal activities.



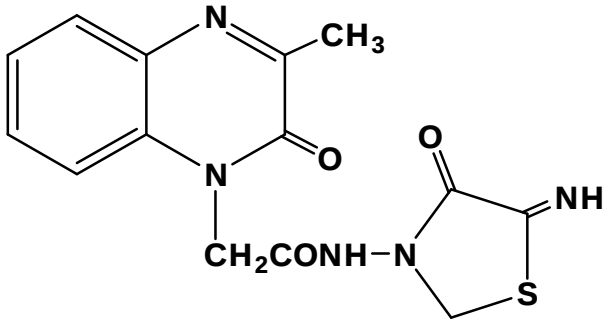
(15)

In the year 1990, HamedEad and co-workers[92] reported a cycloaddition reaction of series of 5-(2-thienyl) methylene **(16)** derivatives of thiazolidinone-4-thiones. The synthesized compounds were screened for antimicrobial activities. The results of biological activity expressed that all compounds were more potent in nature.



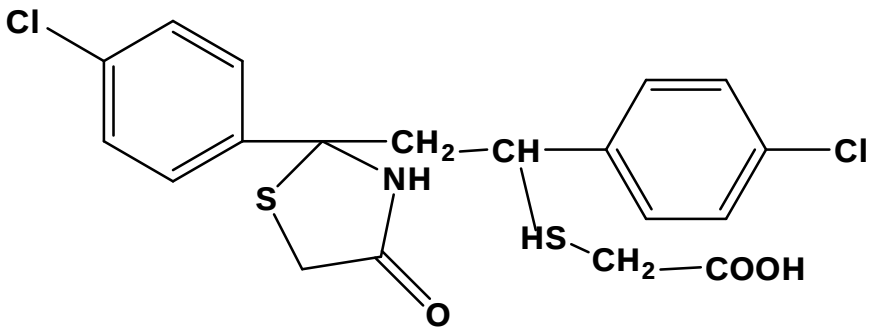
(16)

Preparation of quinoxaline derivatives containing thiazolidinone **(17)** residue as a potent antibacteial and antifungal agent was reported by Afaf K Ansary and co-workers[93] in the year 1995. All the compounds were found to exhibit significant antimicrobial activity.



(17)

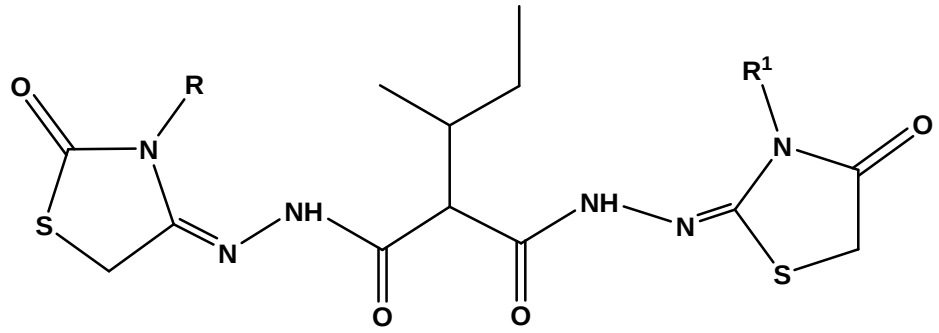
Sayed R and co-workers[94] in the year 1999 synthesized a novel compound 2-[2-carboxy methylthio-2-(4-chlorophenyl) ethyl]-2-(4-chlorophenyl)-4-thiazolidinone **(18)** and studied its biological potency.



(18)

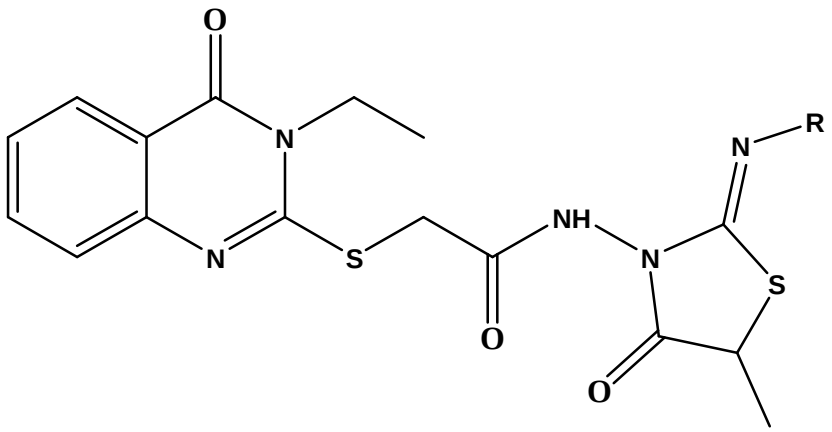
2.5. ANTICONVULSANT ACTIVITY

In the year 1996, Ulusoy and co-workers[95] have reported the synthesis, characterization and anticonvulsant evaluation of bis-thiazolidin-4-one **(19)**. The results of biological activity indicate that substitution of phenyl group at 3rd position and alkyl group at 4th position results in potent activity.



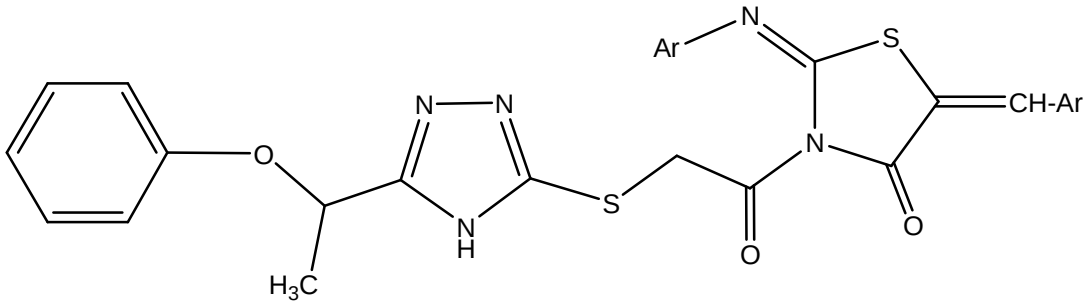
(19)

Aysel and co-workers[96] in 2005 have synthesized and isolated a new series of 2,3-regioisomeric substituted-4-thiazolidinones **(20)**. These compounds were screened for their anticonvulsant activity. The anticonvulsant data showed that substitution at 3rd position favors pronounced activity. These compounds were found to possess good anticonvulsant activity.



(20)

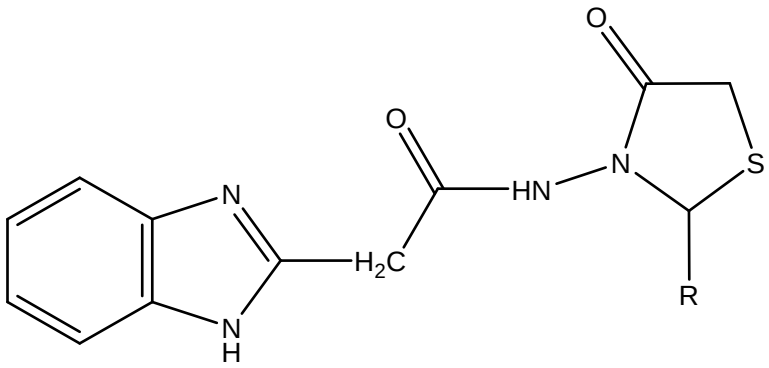
Kailash and co-workers[97] in the year 2007 reported the new series of triazole substituted thiazolidinone derivatives **(21)**. These compounds were evaluated for their neurotoxicity and anticonvulsant activity in two animal models of seizures. The results of screening data shown that, three compounds exhibited excellent anticonvulsant activity.



(21)

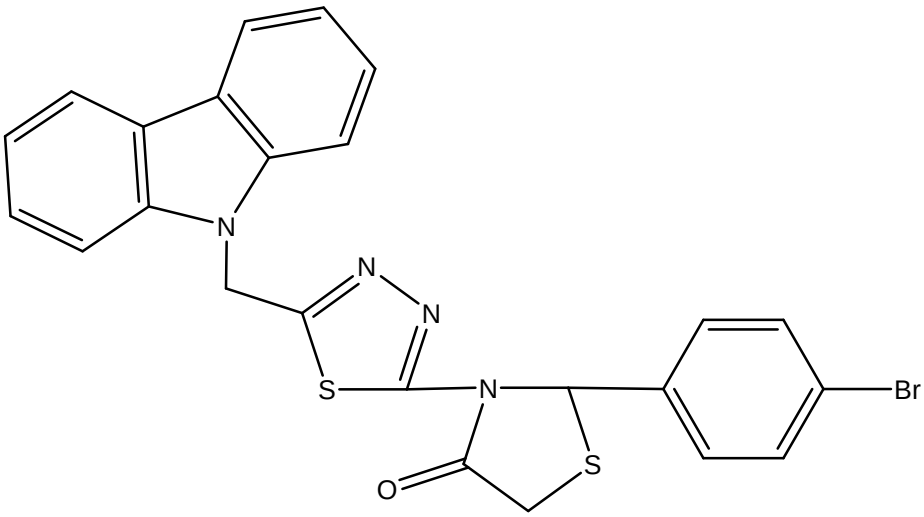
Huger and coworkes[98] in the year 2010 have synthesized a group of thiazolidinones containing 2-mercapto benzimidazole moiety **(22)** and screened them for *in-vivo*

anticonvulsant activity by maximal electroshock (MES) model. The activity data reveals that all the synthesized compounds were found to possess potent anticonvulsant activity.



(22)

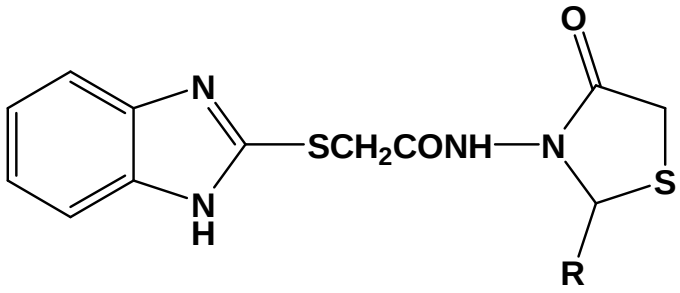
In the same year synthesis and anticonvulsant activity of novel substituted thiadiazolylazetidinonyl derivatives **(23)** were reported by Saxena and co-workers[99]. The activity data concludes that among the synthesized compounds, some of the title compounds exhibited promising anticonvulsant activity.



(23)

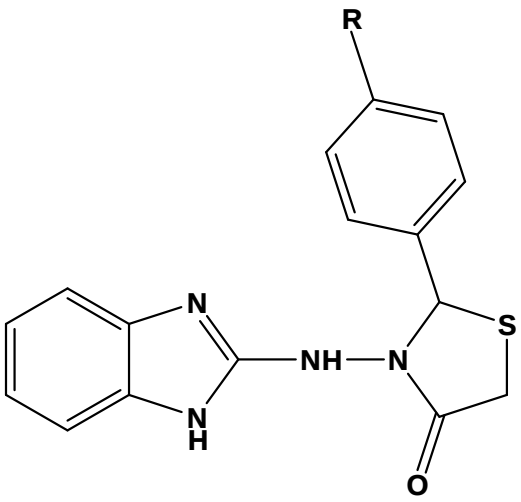
Rangappa and co-workers[100] in the same year reported synthesis of group of thiazolidin-4-ones and 1,3,4-oxadiazoles containing mercapto benzimidazoles**(24)**. The synthesized compounds were screened for *in-vivo* anticonvulsant activity by MES model and

antidiabetic activity. All the compounds were exhibited potent anticonvulsant and antidiabetic activities.



(24)

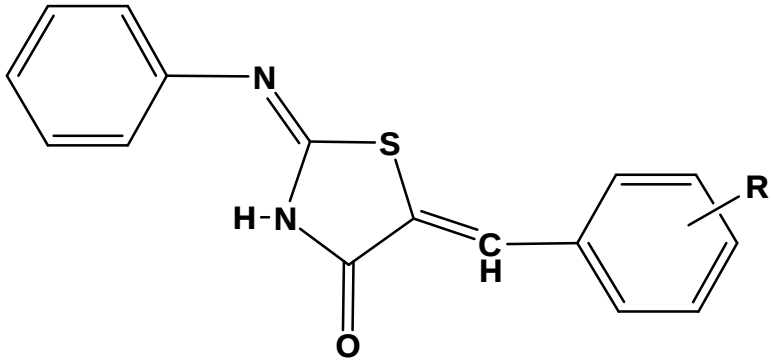
In the year 2011, Ganesh Akula and co-workers[101] prepared a series of benzimidazolyl amino thiazolidin-4-ones **(25)**. These compounds were screened for anticonvulsant activity by the MES induced seizure model. All the compounds were significantly showed their anticonvulsant activity similar to that of standard.



(25)

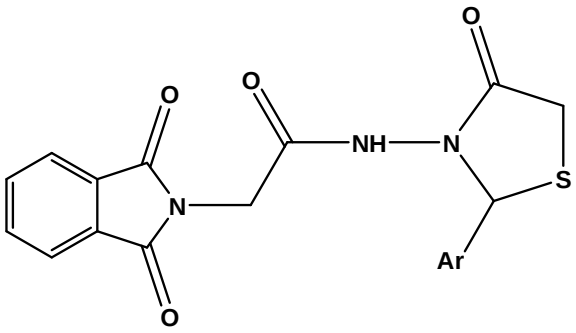
Tejprakash and co-workers[102] in the same year have synthesized and characterized a series of substituted 5-ethylidene-2-pheny limino-4-thiazolidinones **(26)**. These compounds were screened for their anticonvulsant activity. From the results they concluded that

substitution in 5th position with electrophilic groups such as nitro group shows good anticonvulsant activity than the nucloephilic groups such as methoxy and methyl group.



26)

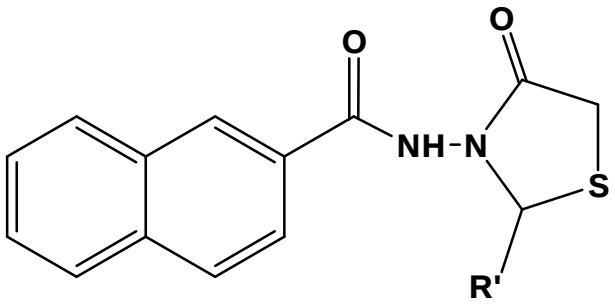
Nikalje and co-workers[103]in the same year reported a series of 2-dioxoisoindolin-N-4-oxo substituted thiazolidinylacetamide derivatives **(27)**. All the compounds were evaluated for anticonvulsant and CNS depressant activity in mice by MES and pentylenetetrazole induced seizure model and also screened their neurotoxicity. The results reveals that all the compounds were showed protection against MES test to inhibit seizure.



(27)

In the year 2012, Indulatha *et al.* [104] have reported the synthesis of novel *N*-4-oxo-2-aryl and heteroaryl substituted thiazolidin-3-yl-3-carboxamido-2*H*-chromen-2-ones **(28)** as potent anticonvulsant agents. The activity results indicated that all the compounds exhibited

63 percent protection which is an indicative of having ability to prevent seizure spread at the dose level of 100 mg/kg when compared to the standard drug.



(28)

CHAPTER-3

RESEARCH ENVISAGED

3.1 Objective of the Present Work

Thiazolidinones possess a wide spectrum of biological and pharmacological activity due to the presence of nitrogen and sulfur which is considered to be responsible for the structural features to impart their activities.

Despite the optimal use of available anticancer drugs (ACDs), many patients fail to experience therapeutic efficacy and others do so only at the expense of significant toxic side effects. The limitations with the conventional ACDs highlighted the need for developing newer anti-cancer agents with new, less toxic and more effective drugs are required. Thiazolidinones are five membered ring system containing sulphur and nitrogen atom, received a much attention of medicinal chemists due to their potential biological activities. Various substituents' at C-2 and C-3 of thiazolidinone results in potent anticancer activity. Prompted by these reports, we aimed to prepare the following series of 2, 3-disubstituted-Thiazolidinone derivatives as potent anticancer agents.

Hence the specific aims & objectives of the present study are,

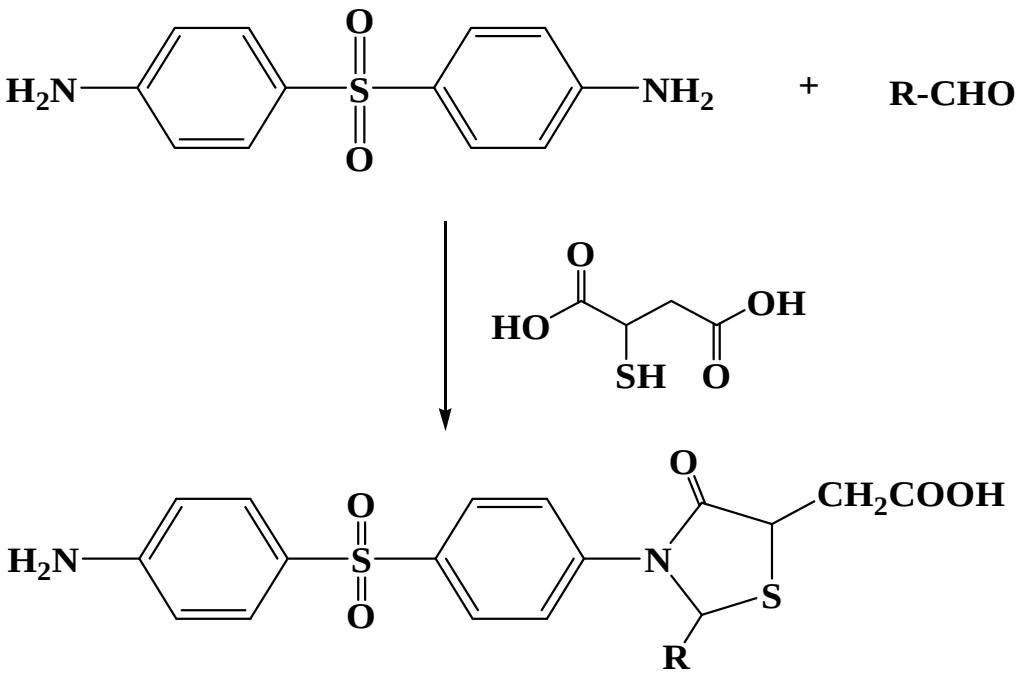
- To synthesize a series of novel 2, 3-disubstituted thiazolidinones.
- To characterize the synthesized compounds by IR, NMR, Mass spectra and elemental analysis.
- To evaluate the test compounds for anti-cancer activity by using human cervical cancer cell line (HeLa) by MTT assay method.

The title compounds are planned to synthesize by using the following synthetic routes mentioned in the following Schemes.

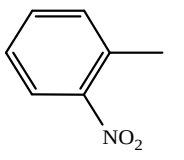
Scheme

Synthesis of 2-(3- (4- (4-aminophenylsulfonyl) phenyl)-2-(2-phenylsubstituted)-4 oxothiazolidin-5-yl) acetic acid **(TD1-7).**

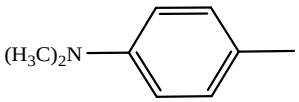
SCHEME



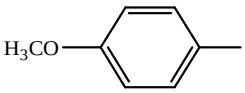
R=



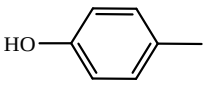
TD1



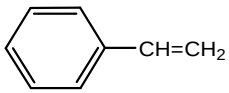
TD 2



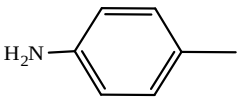
TD 3



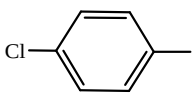
TD 4



TD 5



TD 6



TD 7

CHAPTER–4
4.1 EXPERIMENTAL WORK

4.1.1 MATERIALS AND METHODS

Melting points (mp) were taken in open capillaries on Thomas Hoover melting point apparatus and are uncorrected. The IR spectra were recorded in film or in potassium bromide disks on a Perkin-Elmer 398 spectrometer. The ^{1}H spectra were recorded on a DPX-500 MHz Bruker FT-NMR spectrometer. The chemical shifts were reported as parts per million (δ ppm) tetramethylsilane (TMS) as an internal standard. Mass spectra were obtained on a JEOL-SX-102 instrument using fast atom bombardment (FAB positive). Elemental analysis was performed on a Perkin-Elmer 2400 C, H, N analyzer and values were within the acceptable limits of the calculated values. The progress of the reaction was monitored on readymade silica gel plates (Merck) using chloroform-methanol (9:1) as a solvent system. Iodine was used as a developing agent. Spectral data (IR, NMR and mass spectra) confirmed the structures of the synthesized compounds and the purity of these compounds was ascertained by micro analysis. Elemental (C,H,N) analysis indicated that the calculated and observed values were within the acceptable limits (± 0.4%). All chemicals and reagents were obtained from Aldrich (USA), Lancaster (UK) or Spectrochem Pvt.Ltd (India) and were used without further purification.

4.1.1.1 General procedure for synthesis of 2-(5-amino-1,3,4-thiadiazol-2-yl)phenol (TD1-7)

4-(4-aminophenylsulfonyl) benzenamine (2.48gm) (0.01mol) and substituted benzaldehydes (1.47gm) (0.01mol) were dissolved in alcohol (30ml) in a 250ml round bottom flask. To this concentrated sulphuric acid (0.5ml) and dry dioxane (12ml) was added with constant stirring. To this mixture, 2-mercapto succinic acid (1.5 gm) (0.01mol) in 12ml of dry dioxane was added slowly and refluxed for 3 hr at 80^0C with occasional shaking. The reaction completion was monitored by thin layer chromatography. The solid mass separated was poured in to ice cold water and filtered. The solid was neutralized with one percent sodium carbonate solution, filtered and dried. The residue was recrystallized from methanol.

4.1.1.2 Synthesis of 3-(4-(4-aminophenylsulfonyl) phenyl)-2-(2-nitrophenyl)-4-oxothiazolidin-5-yl) acetic acid (TD1)

Yield	: 2.86 g; 81.0 %
Melting Point	: 216-218 °C
Rf Value	: 0.85 (benzene : ethylacetate(8:2))
Molecular Formula	: $C_{23}H_{19}N_3O_7S_2$
Molecular Weight	: 513(M+)
IR (KBr) cm^{-1}	: 3520 (OH), 3290 (NH_2), 3045 (Ar-CH), NO_2 (1534),1620 (C=N Str), SO_2(688) 675 (C-S-C).
^{1}H NMR ($CDCl_3$) δ ppm	:^{1}H NMR ($CDCl_3$) δ (ppm): 2.82-3.07 (d, 1H, CH_2), 3.80 (d,1H,CH),4.01(s,2H, NH_2), 6.63 (d, *J = 8.0 Hz*, 2H, Ar-H), 7.27-7.95 (m, *J =8.0Hz*, 8H, Ar-H).
Elemental Analysis	
Calculated	: C, 53.79; H, 3.73; N, 8.18.
Found	: C, 53.76; H, 3.71; N, 8.17.

4.1.1.3 Synthesis of 3-(4-(4-aminophenylsulfonyl)phenyl)-2-(4-(dimethylamino)phenyl)-4-oxothiazolidin-5-yl)acetic acid (TD 2).

Yield	: 2.90 g; 89.0 %
Melting Point	: 245-247 °C
Rf Value	: 0.72 (benzene:ethylacetate(8:2))
Molecular Formula	: $C_{25}H_{25}N_3O_5S_2$
Molecular Weight	: 511(M+)
IR (KBr) cm^{-1}	: 3516 (OH), 3290 (NH_2), 3045 (Ar-CH), 1710 (C=O),1622 (C=NStr), 676 (C-S-C),1289 ($N(CH3)_2$),(1191)SO_2.
^{1}H NMR ($CDCl_3$) δ ppm	:^{1}H NMR ($CDCl_3$) δ (ppm): 2.82-3.07 (d, 2H, CH_2), 2.85 (d, 6H,$(CH_3)_2$,3.80 (d,1H,CH),4.01(s,2H, NH_2), 6.63 (d, *J = 8.0 Hz*, 2H, Ar- H), 7.27 (d, *J =7.5Hz*, 2H, Ar-H), 7.65 (d, *J = 7.0 Hz*, 2H, Ar-H), 7.95 (d, *J = 7.0 Hz*, 2H, Ar-H).
Elemental Analysis	
Calculated	: C, 58.69; H, 4.93; N, 8.21.
Found	: C, 58.67; H, 4.91; N, 8.20.

4.1.1.4 Synthesis of 3-(4-(4-aminophenylsulfonyl)phenyl)-2-(4-methoxyphenyl)-4-oxothiazolidin-5-yl) acetic acid (TD 3).

Yield	: 2.68 g; 79.0 %
Melting Point	: 227-229 °C
Rf Value	: 0.78 (benzene:ethylacetate(8:2))
Molecular Formula	: $C_{24}H_{22}N_2O_6S_2$
Molecular Weight	: 498(M+)
IR (KBr) cm^{-1}	: 3516 (OH), 3290 (NH_2), 3045 (Ar-CH), 1622 (C=N Str), 676 (C-S-C), 2816 (OCH_3),
^1H NMR ($CDCl_3$) δ ppm	:^1H NMR ($CDCl_3$) δ (ppm): 2.82-3.07 (d, 2H, CH_2), 3.73(s, 3H, CH_3),3.80 (d,1H,CH),4.01(s,2H, NH_2), 6.63 (d, *J = 8.0 Hz*, 2H, Ar- H), 7.27 (d, *J =7.5Hz*, 2H, Ar-H), 7.65 (d, *J = 7.0 Hz*, 2H, Ar-H), 7.95 (d, *J = 7.0 Hz*, 2H, Ar-H).
Elemental Analysis	
Calculated	: C, 57.82; H, 4.45; N, 5.62.
Found	: C, 57.80; H, 4.45; N, 5.61

4.1.1.5 Synthesis of (3-(4-(4-aminophenylsulfonyl) phenyl)-2-(4-hydroxyphenyl)-4-oxothiazolidin-5-yl) acetic acid (TD 4).

Yield	: 2.47 g; 81.0 %
Melting Point	: 197-199 °C
Rf Value	: 0.76 (benzene: ethyl acetate(8:2))
Molecular Formula	: $C_{23}H_{20}N_2O_6S_2$
Molecular Weight	: 484(M+)
IR (KBr) cm^{-1}	: 3522 (OH, broad), 3287 (NH_2), 3045 (Ar-CH), 1620 (C=N Str), 675 (C-S-C).
^1H NMR ($CDCl_3$) δ ppm	:^1H NMR ($CDCl_3$) δ (ppm): 2.82-3.07 (d, 2H, CH_2), 3.80 (d,1H,CH),4.01(s,2H, NH_2), 6.63 (d, *J = 8.0 Hz*, 2H, Ar- H), 7.27 (d, *J =7.5Hz*, 2H, Ar-H), 7.65 (d, *J = 7.0 Hz*, 2H, Ar-H), 7.95 (d, *J = 7.0 Hz*, 2H, Ar-H), 11.0(s, 1H, OH).
Elemental Analysis	
Calculated	: C, 57.01; H, 4.16; N, 5.78
Found	: C, 57.00; H, 4.15; N, 5.77

4.1.1.6. Synthesis of (3-(4-(4-aminophenylsulfonyl)phenyl)-4-oxo-2-styrylthiazolidin-5-yl) acetic acid (TD 5).

Yield : 2.12 g; 64.0 %

Melting Point : 245-247 °C

Rf Value : 0.64 (benzene: ethyl acetate(8:2))

Molecular Formula : $C_{25}H_{22}N_2O5S_2$

Molecular Weight : 494(M+)

IR (KBr) cm^{-1} : 3508 (OH), 3286 (NH_2), 3048 (Ar-CH), 1618 (C=N Str), 674 (C-S-C),(1510) CH=CH.

^1H NMR ($CDCl_3$) δ ppm :^1H NMR ($CDCl_3$) δ (ppm): 2.82-3.07 (d, 2H, CH_2), 3.80 (d,1H,CH),4.01(s,2H, NH_2), 6.63 (d, *J = 8.0 Hz*, 2H, Ar- H), 7.21 (d, *J =7.5Hz*, 2H, Ar-H), 7.27 (d, *J =7.5Hz*, 2H, Ar-H), 7.30 (d, *J =7.5Hz*, 2H, Ar-H), 7.65 (d, *J = 7.0 Hz*, 2H, Ar-H), 7.95 (d, *J = 7.0 Hz*, 2H, Ar-H), 10.2(s, 1H, OH).

Elemental Analysis

Calculated : C, 60.71; H, 4.48; N, 5.66

Found : C, 60.69; H, 4.47; N, 5.65

4.1.1.7 Synthesis of (3-(4-(4-aminophenylsulfonyl)phenyl)-2-(4-aminophenyl)-4-oxothiazolidin-5-yl)acetic acid (TD 6).

Yield : 2.32 g; 76.0 %

Melting Point : 187-189 °C

Rf Value : 0.72 (benzene: ethyl acetate(8:2))

Molecular Formula : $C_{23}H_{21}N_3O_5S_2$

Molecular Weight : 483(M+)

IR (KBr) cm^{-1} : 3310 (NH_2, broad), 3042 (Ar-CH), 1619 (C=N Str), 672 (C-S-C).

^1H NMR ($CDCl_3$) δ ppm :^1H NMR ($CDCl_3$) δ (ppm): 2.82-3.07 (d, 2H, CH_2), 3.80 (d,1H,CH),4.08(d ,2H, NH_2), 6.34 (2, *J = 8.0 Hz*, 2H, Ar- H), 6.63 (d, *J = 8.0 Hz*, 2H, Ar- H), 7.27 (d, *J =7.5Hz*, 2H, Ar-H), 77.65 (d, *J = 7.0 Hz*, 2H, Ar-H), 7.95 (d, *J = 7.0 Hz*, 2H, Ar-H), 10.3(s, 1H, OH).

Elemental Analysis

Calculated : C, 57.13; H, 4.38; N, 8.69

Found : C, 57.11; H, 4.37; N, 8.68

4.1.1.8 Synthesis of (3-(4-(4-aminophenylsulfonyl)phenyl)-2-(4-chlorophenyl)-4-oxothiazolidin-5-yl) acetic acid (TD 7).

Yield : 2.15 g; 74.0 %

Melting Point : 177-179 °C

Rf Value : 0.70 (benzene: ethyl acetate (8:2))

Molecular Formula : $C_{23}H_{19}ClN_2O_5S_2$

Molecular Weight : 502(M+), 504(M+)

IR (KBr) cm^{-1} :3298 (NH_2), 3040 (Ar-CH), 1617 (C=N Str), 670 (C-S-C),688(C-Cl).

^1H NMR ($CDCl_3$) δ ppm :^1H NMR ($CDCl_3$) δ (ppm): 2.82-3.07 (d, 2H, CH_2), 3.80 (d,1H,CH),4.01(s,2H, NH_2), 6.63 (d, *J = 8.0 Hz*, 2H, Ar- H), 7.00 (d, *J =7.5Hz*, 2H, Ar-H), 7.15 (d, *J =7.5Hz*, 2H, Ar-H), 7.27 (d, *J =7.5Hz*, 2H, Ar-H), 7.65 (d, *J = 7.0 Hz*, 2H, Ar-H), 7.95 (d, *J = 7.0 Hz*, 2H, Ar-H), 10.2(s, 1H, OH).

Elemental Analysis

Calculated : C, 54.92; H, 3.81; Cl, 7.05; N, 5.57 .

Found : C, 54.90; H, 3.80; Cl, 7.04; N, 5.56 .

4.2 CHROMATOGRAPHY STUDIES OF SYNTHESIZED COMPOUNDS

4.2.1 THIN LAYER CHROMATOGRAPHY

Thin Layer Chromatography or TLC is a solid-liquid form of chromatography here the stationary phase is a polar absorbent and the mobile phase can be a single solvent or Combination of solvents. TLC is in expensive technique and quick that can be used for determine the number of components in a mixture, verify a substance's identity, monitor the process of a reaction, determine appropriate condition for column chromatography, analyze the fractions obtained from column chromatography.

4.2.1.1 MATERIALS AND METHODS

1. Preparation of plates

Silicagel G was mixed in a glass mortar to smooth consistency with the requisite amount of water and slurry was quickly transferred to hespreader. The mixtures have been spread over the plates in thickness of 0.2mm and allow setting in to a suitable holder and after 30 minutes; plates were dried at $120^{O}C$, for further activation of the absorbent.

2. Sample application

About 2 mm of absorbent from the edge of plate was removed to gives sharply defined edges. 2-5µl volumes of synthesized compounds were spotted with the help of capillary tubes, just above 1cm of the bottom of coated plates.

3. Development chamber

The chromatographic chamber was lined with filter paper dipping in to mobile phase so as to maintain the atmospheric saturation with solvent vapors in the chamber. The solvent front was allowed to rise to distance of about 12cm from the baseline on the plate was removed from the tank and allowed to dry in the air.

4. Solvent system

The choice of best developing solvent is one of the most important decisions in practical TLC by review of literature survey on by knowing nature of compounds, this solvent system used is benzene: ethyl acetate (8:2).

5. Detection of components

The spots were visualized under Iodine chamber.

4.2.2 COLUMN CHROMATOGRAPHY

Purification of synthesized derivatives was done by column chromatography.

Materials

1. Glass column of size 45cm x 3cm.

2. Silicagel for column chromatography 60-120 mesh size.

3. Eluting solvent system benzene :ethylacetate (8:2).

Preparation of column

The silica gel 60-120 mesh size was made in to slurry with the above solvent system. The bottom of the column was plugged with little glass wool. Then the slurry was poured in to the column, which is filled with solvent after two third of the column areas were filled with slurry. It was set aside for 30 minutes and eluting solvent was passed through column for several time ensure good packing of the column. After the adsorbents are settled, a filter paper was kept to prevent disturbance of the two player of the adsorbent as fresh mobile phase to be added to column for the process of elution. The fractions were collected for every 5m land analyzed for the presence of different of similar compound by running TLC and then allow evaporating to get the residue.

4.3. PHARMACOLOGICAL SCREENING

4.3.1. *IN-VITRO* ANTI-CANCER ACTIVITY

Tissue culture has been used to screen may anti-cancer drugs since there is clear correlation between the in vitro and in vivo activities of potential chemotherapeutic agents. There is scientific justification for cytotoxicity testing in tissue, since animal models are in many ways in adequate for predicting the effects of chemicals on humans since there are many metabolic differences between species[61-63].

Cytotoxicity studies involve the analysis of morphological damage or inhibition of zone of outgrowth induced by the chemicals tested.

ASSAY FOR PROLIFERATION STUDIES

IN VITRO ANTI CANCER ACTIVITY

The human cervical cancer cell line (HeLa) was obtained from national center for cell science (NCCS) pune. The HeLa cells were grown in Eagles Minimum Essential Medium containing 10% fetal bovine serum (FBS) and maintained at 37°C, 5% CO_2, 95% air and 100% relative humidity. Maintenance cultures were passaged weekly, and the culture medium was changed twice a week.

Toxicity of test compound in cells was determined by MTT assay based on mitochondrial reduction of yellow MTT tetrazolium dye to a highly colored blue formazan product[40].

Assay for Proliferation Studies - MTT Assay

Principle

MTT [(3-(4,5-dimethyl thiazol-2yl)-2,5diphenyl tetrazolium bromide] measures the metabolic activity of the viable cells. The assay can be performed entirely in a microtiterplate (MTP). It is suitable for measuring cell proliferation, Cell viability or Cytotoxicity. The reaction between MTT and mitochondrial dehydrogenase produces water-insoluble formazan salt. This method involves culturing the cells in a 96 well microtiterplate and then incubating with MTT solution for approximately 2 hours. During incubation period, viable cells convert MTT to a water insoluble formazan dye. The formazan dye in the MTP is solubilized and quantified with

an ELISA plate reader. The absorbance directly correlates with the cell number. This is applicable for adherent cells cultured in MTP.

Materials for MTT assay

- The human cervical cancer cell line (**HeLa**) Eagles Minimum Essential Medium containing 10% fetal bovine serum (FBS).
- Phosphate buffered saline (PBS)
- Dimethyl sulphoxide (DMSO)
- MTT [(3-(4,5-dimethylthiazol-2yl)-2,5 di phenyl tetrazolium bromide]CO_2 incubator (WTC Binder, Germany)
- Laminar air flow cabin (Klenzaids, Chennai, India).
- Refrigerated centrifuge (Biofuge fresco, Heraeus, Germany).
- ELISA-reader (For MTP) Anthos 2010, Germany).
- Deep freezer (Polar Angelantioni Industries, Italy).
- Ultrazonic bath (Transonic [460/H], by Elma, Germany].
- Vaccum pump (Zenith [model: PDF-2-2.5], Mumbai, India).
- Pipettes (Eppendoff, Hamburg, Germany).
- Culture plates
- Centrifuge tubes
- Aerosol resistant tips
- Flat-bottomed 96-MTP
- Tissue culture grade

Cell treatment procedure

Cell treatment procedure the monolayer cells were detached with trypsin-ethylene diamine tetraacetic acid (EDTA) to make single cell suspensions and viable cells were counted using a hemocytometer and diluted with medium with 5% FBS to give final density of 1x105 cells/ml. one hundred microlitres per well of cell suspension were seeded into 96-well plates at plating density of 10,000 cells/well and incubated to allow for cell attachment at 37^0C, 5% CO_2, 95% air and 100% relative humidity.

After 24 h the cells were treated with serial concentrations of the extracts and fractions. They were initially dissolved in neat dimethylsulfoxide (DMSO) and further diluted in serum free medium to produce five concentrations. One hundred microlitres per well of each concentration was added to plates to obtain final concentrations of 100, 10, 1.0 and 0.1 μM. The final volume in each well was 200 μl and the plates were incubated at 37^0 C, 5% CO_2, 95% air and 100% relative humidity for 48h. The medium containing without samples were served as control. Triplicate was maintained for all concentrations.

Procedure

***In-vitro* anticancer screening**

The human cervical cancer cell line (**HeLa**) was obtained from National Centre for Cell Science (NCCS), Pune. The cells were grown in Eagles Minimum Essential Medium containing 10% fetal bovine serum (FBS)[63].

For screening experiment, the cells were seeded into 96-well plates in 100µl of medium containing 5 % FBS, at plating density of 10,000 cells/well and incubated at 37 ^{0}C, 5 % CO_2, 95 % air and 100 % relative humidity for 24 hours prior to addition of samples. The samples were solubilized in Dimethylsulfoxide and diluted in serum free medium. After 24 hours, 100 µl of the medium containing the samples at various concentration (eg; 0.063, 0.125, 0.25, 0.5, 1.0 mM etc…) was added and incubated at 37^{0}C, 5% CO_2, 95% air and 100% relative humidity for 48 hours. Triplicate was maintained and the medium containing without samples were served as control[41].

After 48 hours, 15µl of MTT (5mg/ml) in phosphate buffered saline (PBS) was added to each well and incubated at 37 ^{0}C for 4 hours. The medium with MTT was then flicked off and the formed formazan crystals were solubilized in 100µl of DMSO and then measured the absorbance at 570 nm using micro plate reader. The % cell inhibition was determined using the following formula % cell Inhibition= 100 – {(sample) / Abs (control)}× 100.

***Invitro* Cytotoxicity Studies on Human Cervical Cancer Cell line (HeLa)**

PERCENTAGE OF CELLINHIBITION

Table No.2.

Compounds	Concentration	% Cell Inhibition	Compounds	Concentration	% Cell Inhibition
TD1	0.1 µM	1.5342	**TD5**	0.1 µM	1.4112
	1 µM	12.9079		1 µM	13.7176
	10 µM	30.9861		10 µM	23.8976
	100 µM	**62.8578**		100 µM	**51.3006**
TD2	0.1µM	1.0424	**TD6**	0.1µM	1.1895
	1µM	10.4447		1 µM	12.2646
	10 µM	22.9848		10 µM	23.6772
	100 µM	**52.8995**		100 µM	**55.0587**
TD3	0.1µM	1.4579	**TD7**	0.1 µM	1.3342
	1µM	11.0145		1 µM	14.6079
	10 µM	28.2358		10 µM	33.8761
	100 µM	**70.1268**		100 µM	**74.8578**
TD4	0.1 µM	1.4824			
	1 µM	11.6447			
	10 µM	29.9848			
	100 µM	**72.8995**			

Nonlinear regression graph was plotted between % Cell inhibition and Log_{10} concentration and IC_{50} was determined using GraphPad Prism software.

Statistical Analysis

All values are expressed as mean ± SEM. Data were analyzed by non-parametric ANOVA followed by Dunnett's multiple comparison tests, and other data was evaluated using Graph Pad PRISM software. A *p*-value < 0.05 was considered significantly different.

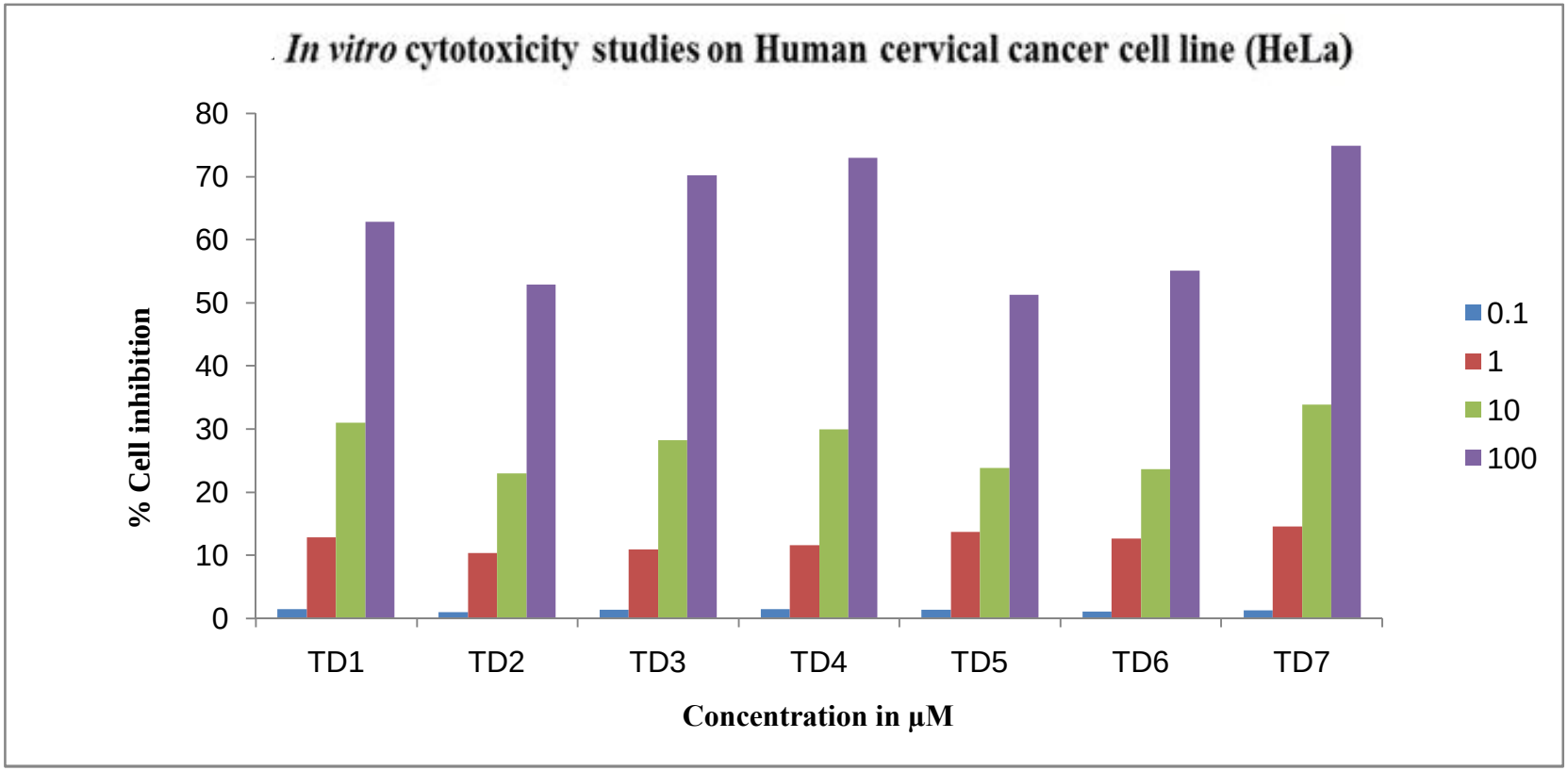
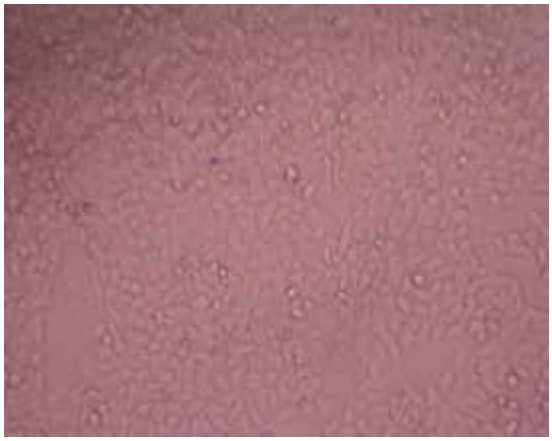
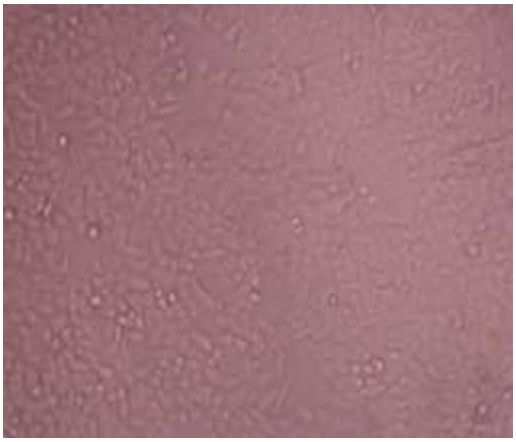


Fig.No.5 Percentage Cell Inhibition on Human Cervical Cancer Cell Line (HeLa)

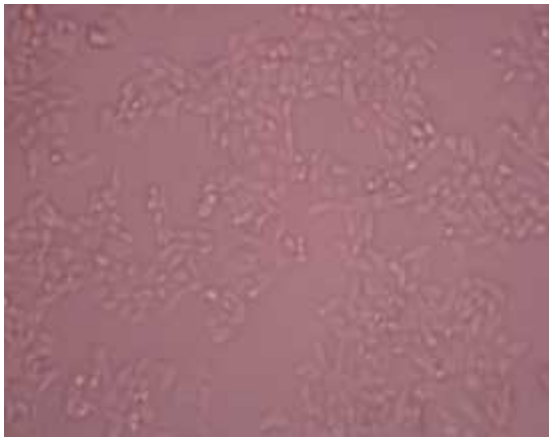
TD1



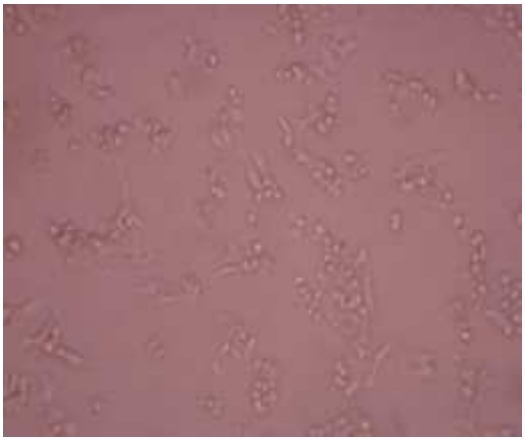
0.1μM



1μM



10μM



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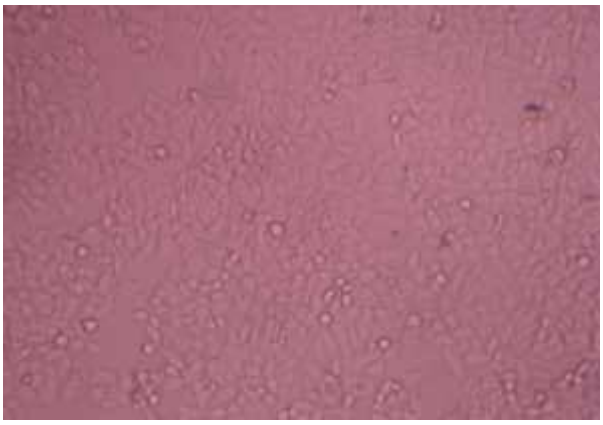
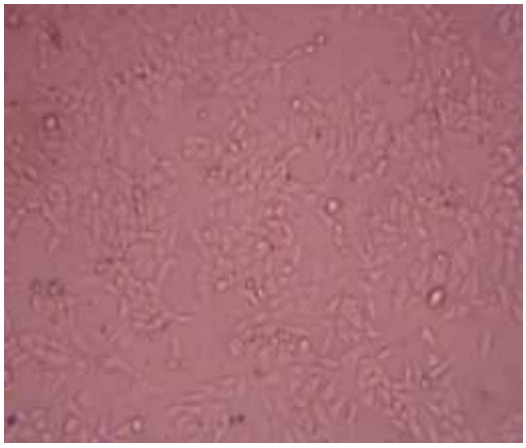


Normal

TD2

0.1μM

1μM



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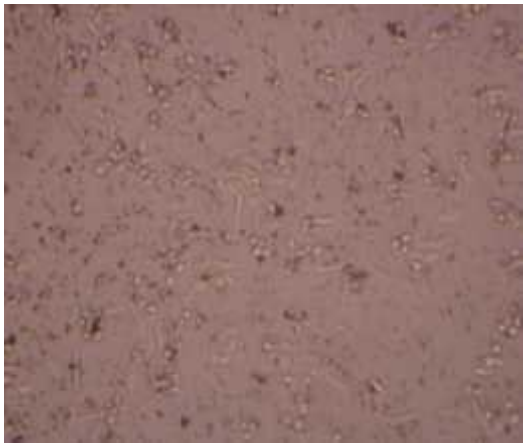

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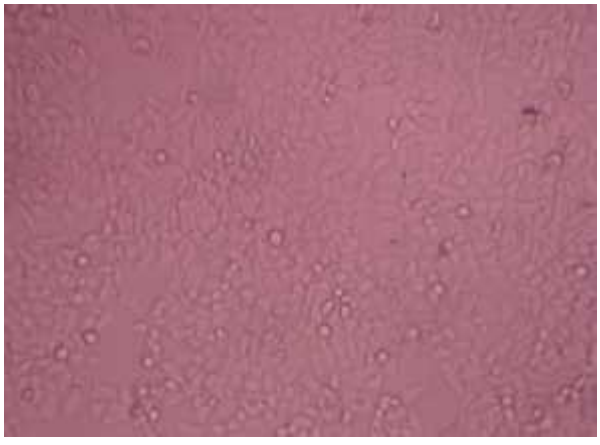

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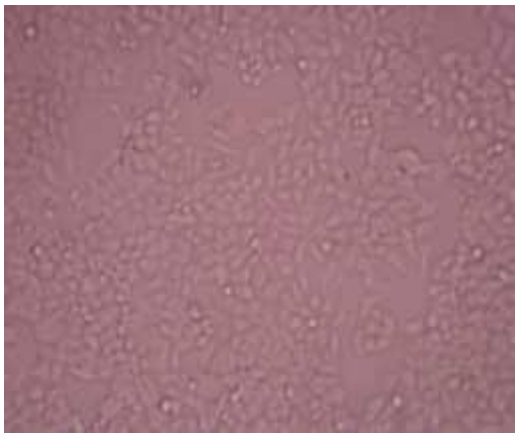
TD3



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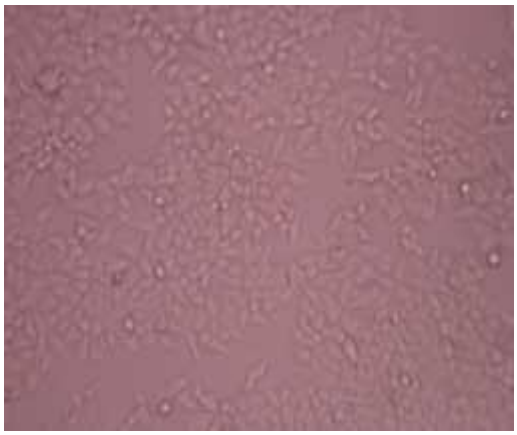

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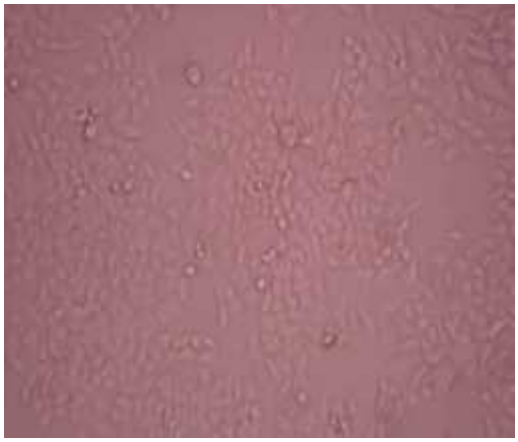

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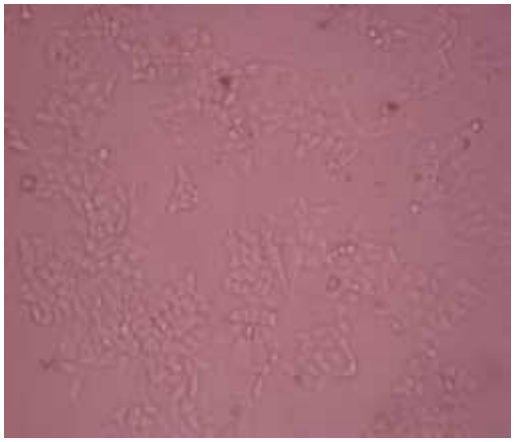

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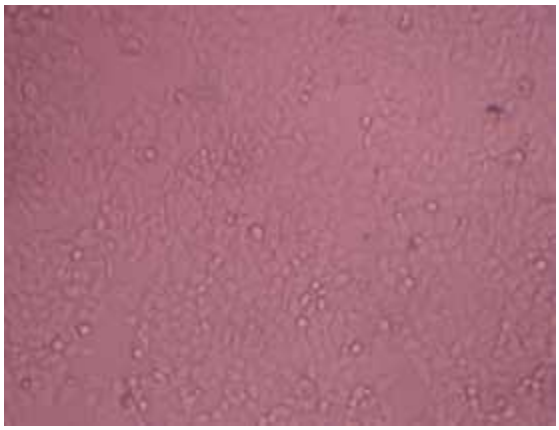
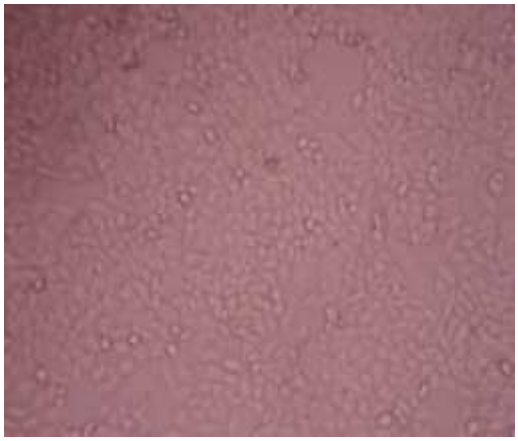


Normal

TD4



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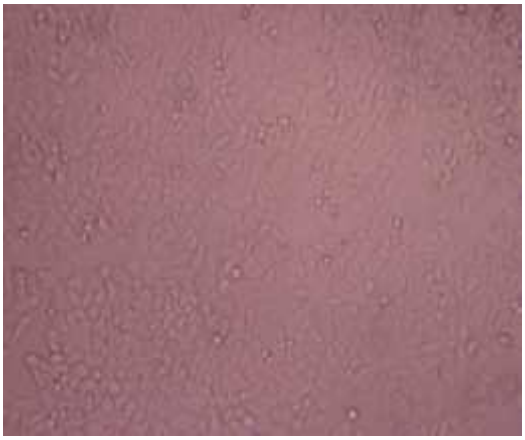

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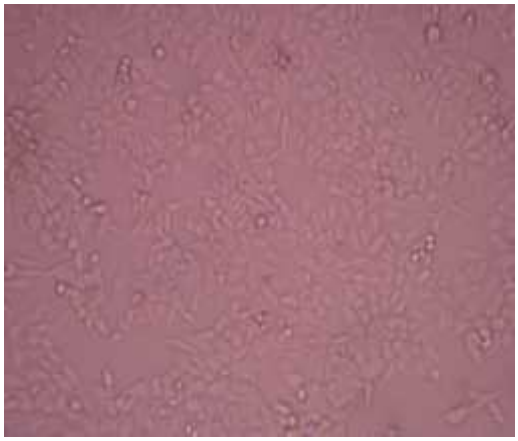

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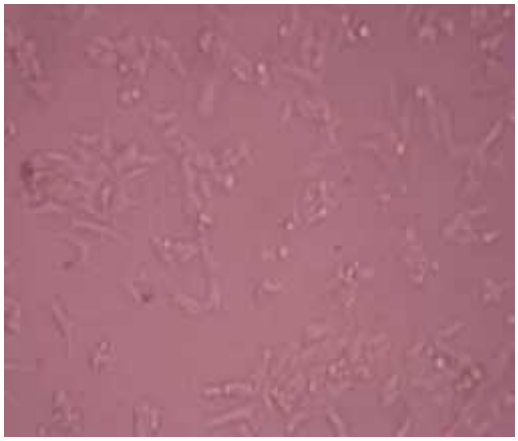

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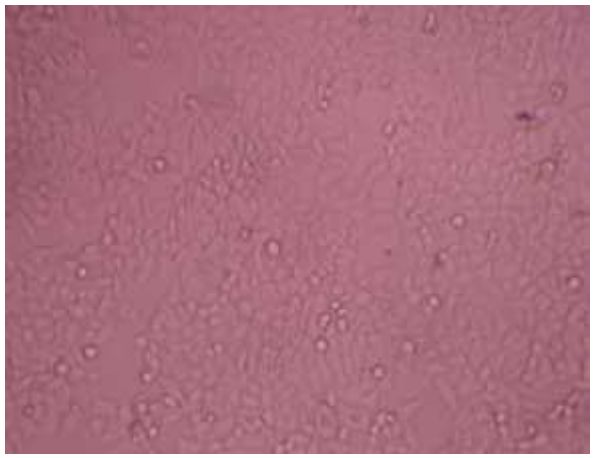
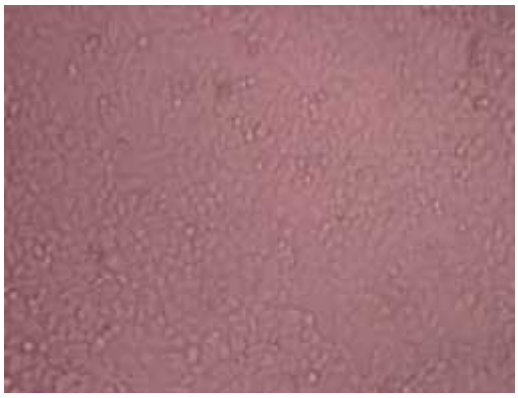


Normal

TD5



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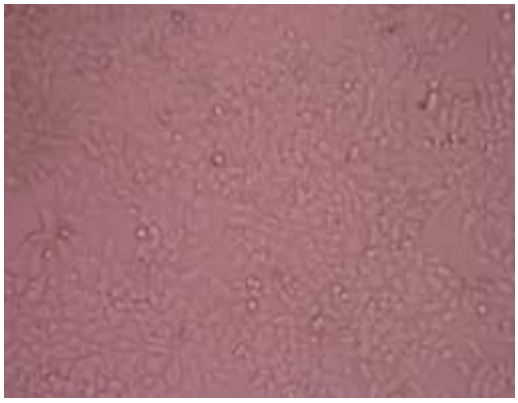

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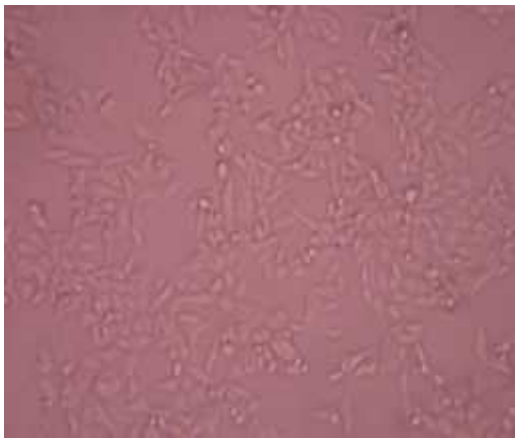

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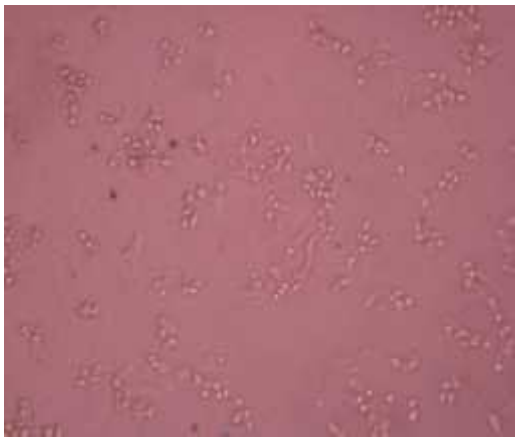

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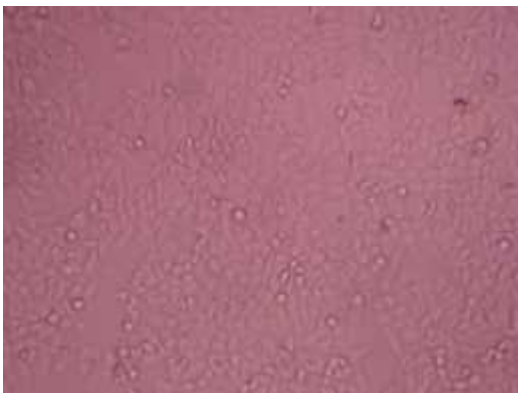
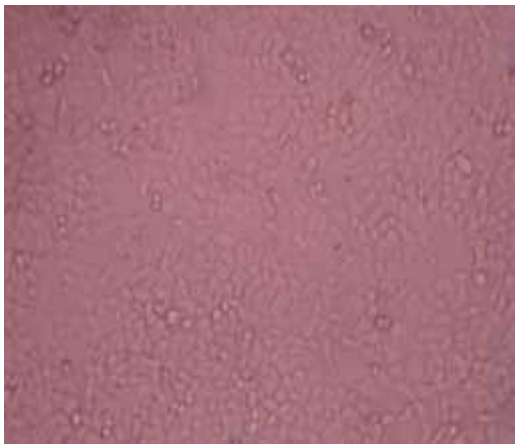


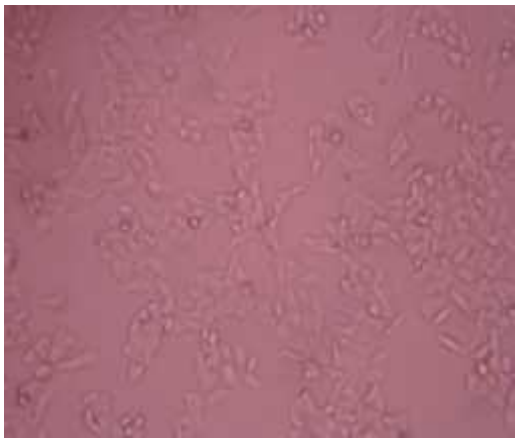
Normal

TD6

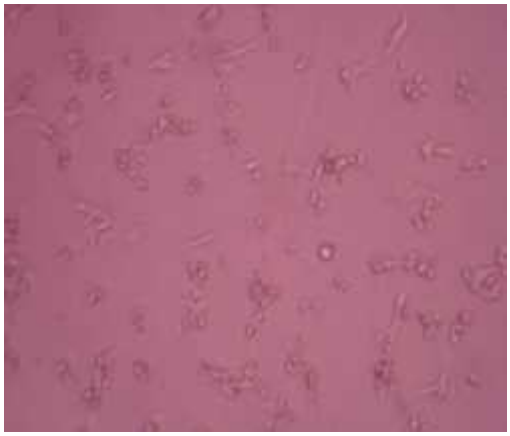


0.1μM

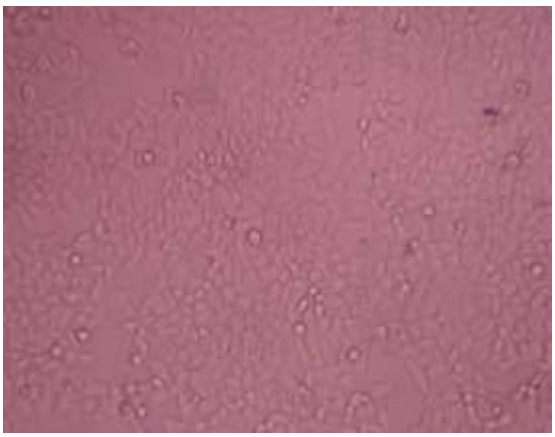
1μM



0μM

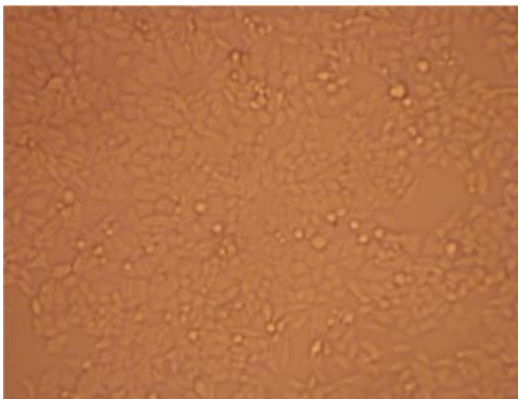


100μ



Normal

TD7



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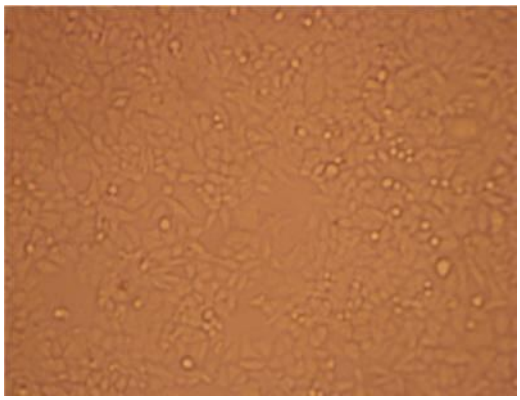
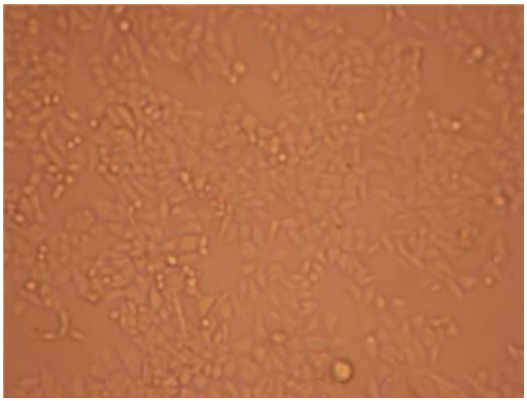
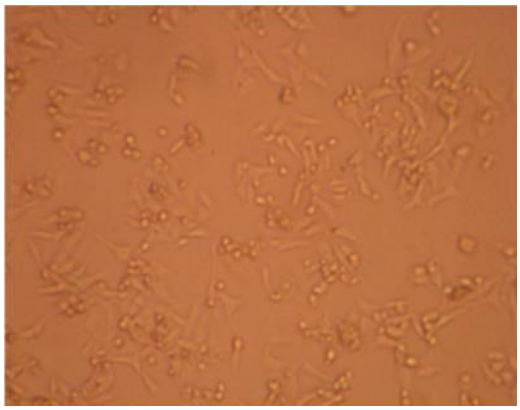


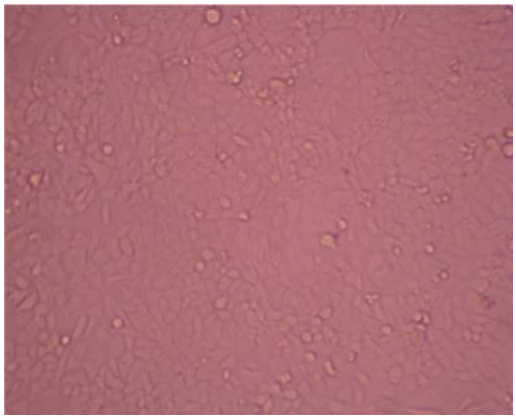
1μM



10 μM



100 μM



Normal

Table No.3: IC_{50} Values of Synthesized Compounds (TD1–TD7)

COMPOUND CODE	IC_{50} (MICRO MOLAR)
TD1	45.70 μM
TD2	66.23 μM
TD3	75.26 μM
TD4	92.36 μM
TD5	68.25 μM
TD6	48.60 μM
TD7	>100 μM

Table No.4 TD1

Concentration (µM)	%Growth Inhibition	IC_{50}	R^2
0.1µM	1.3342	45.70	0.9995
1µM	12.6079		
10µM	33.8761		
100µM	74.8578		

TD1

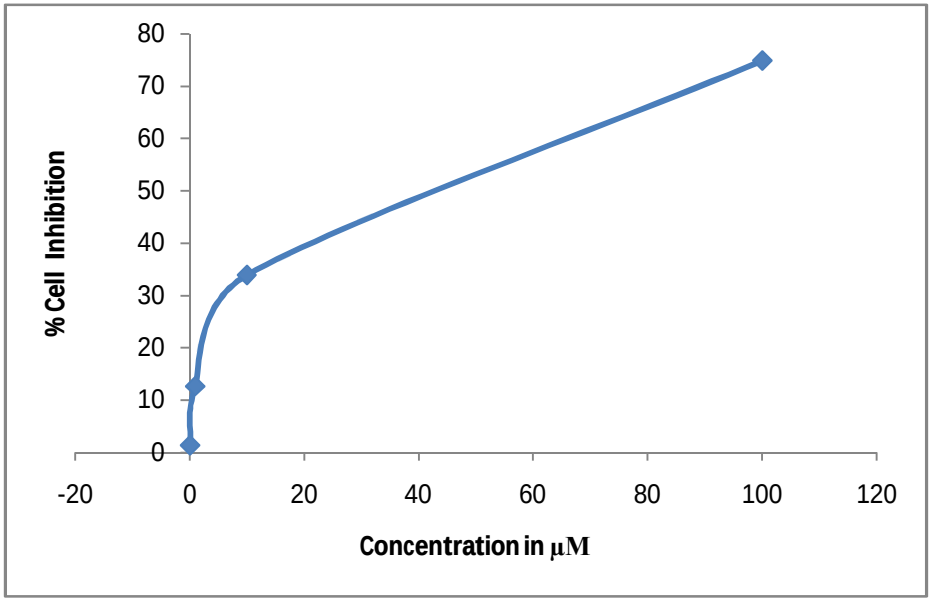


Table No.5 TD2

Concentration (µM)	%Growth Inhibition	IC_{50}	R^2
0.1µM	1.0424	66.23	0.9996
1µM	10.447		
10µM	22.9848		
100µM	52.9885		

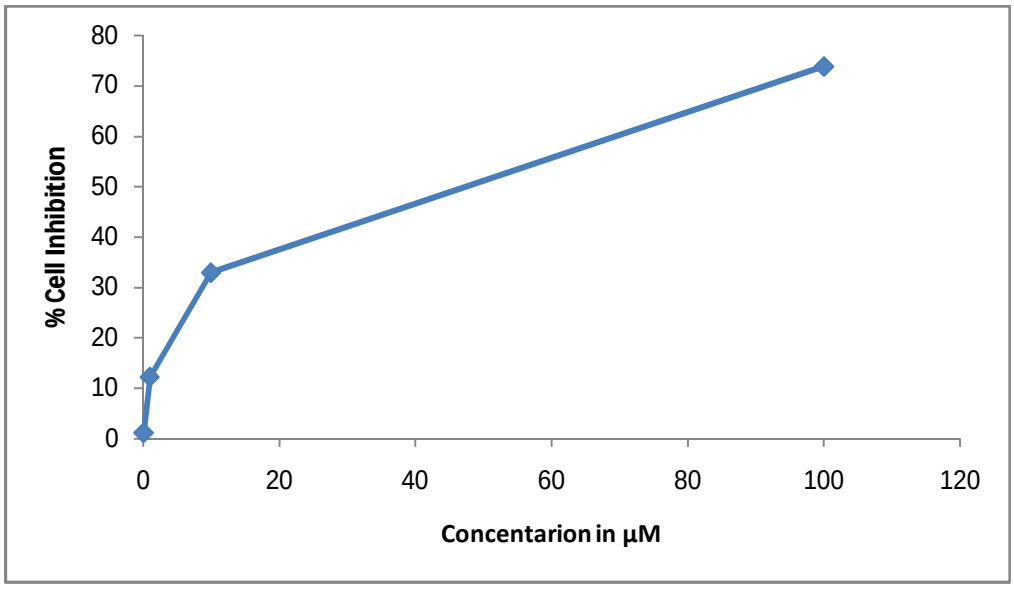


Table No.10 TD3

Concentration (µM)	%Growth Inhibition	IC_{50}	R^2
0.1µM	3.1895	75.26	0.9916
1µM	14.2646		
10µM	23.6772		
100µM	55.0587		

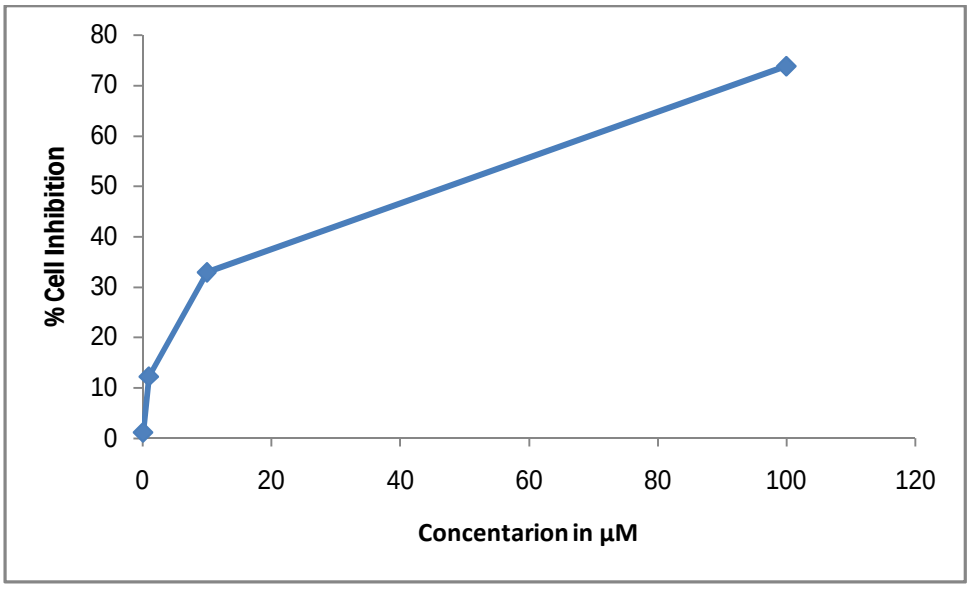


Table No.11 TD4

Concentration (µM)	%Growth Inhibition	IC_{50}	R^2
0.1µM	1.4315	92.36	0.9916
1µM	19.6317		
10µM	35.4864		
100µM	63.8275		

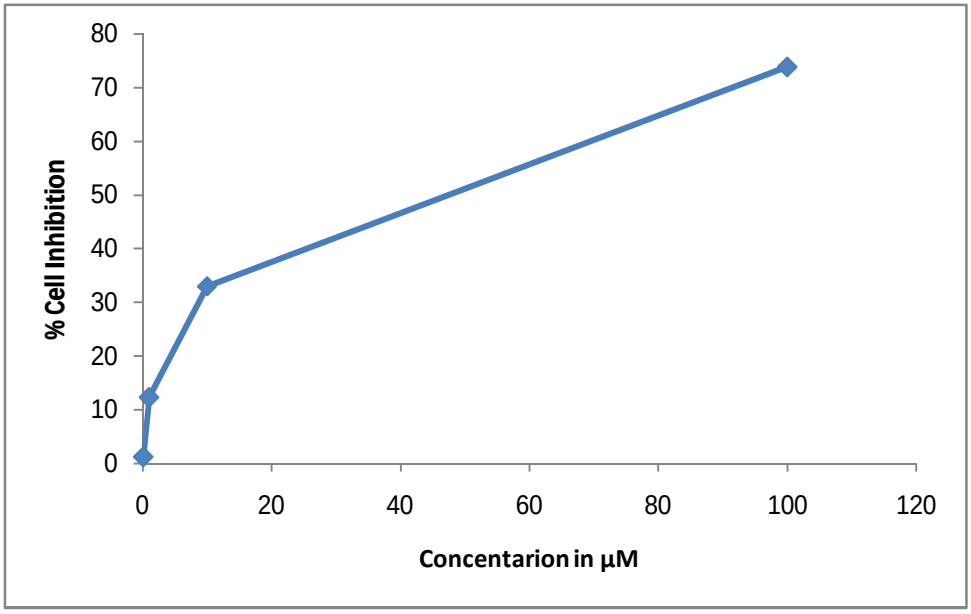


Table No.7 TD5

Concentration (µM)	%Growth Inhibition	IC_{50}	R^2
0.1µM	1.5342	68.25	0.9367
1µM	12.9079		
10µM	30.9861		
100µM	60.8578		

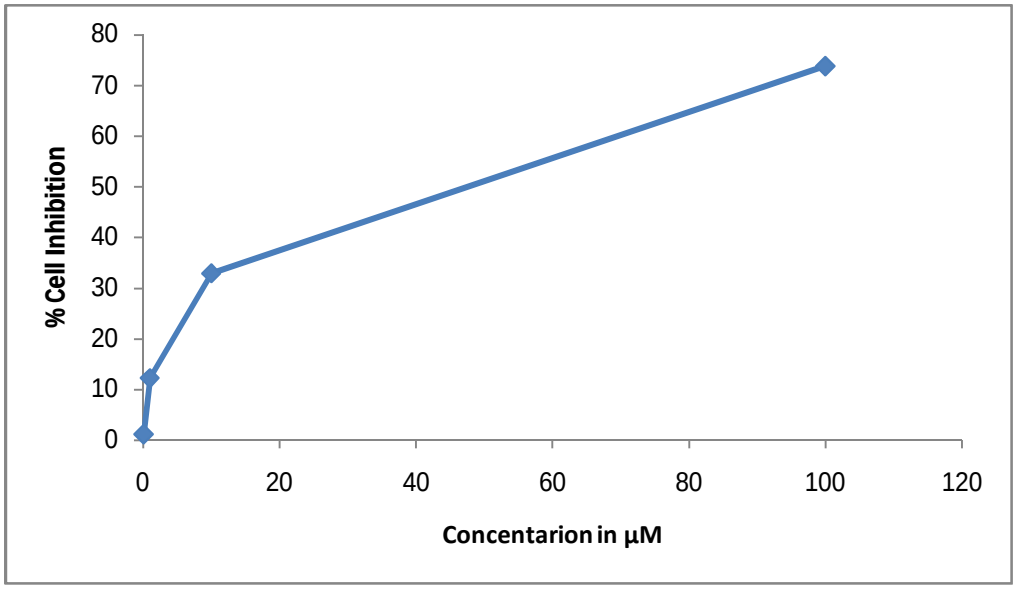


Table No.9 TD6

Concentration (µM)	%Growth Inhibition	IC_{50}	R^2
0.1µM	1.2342	48.60	0.9916
1µM	12.3079		
10µM	32.9861		
100µM	73.8578		

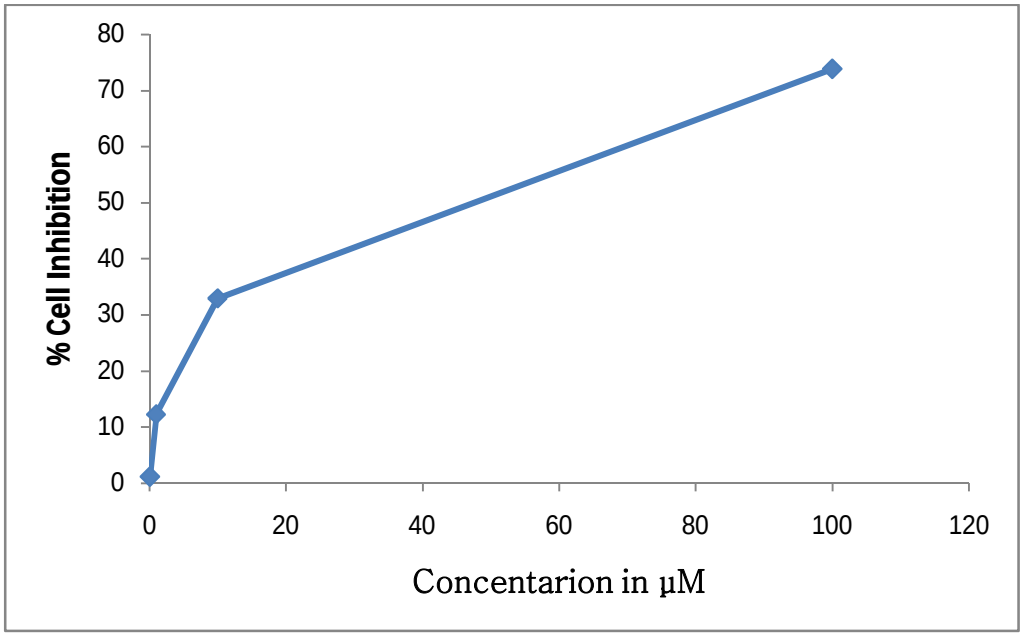
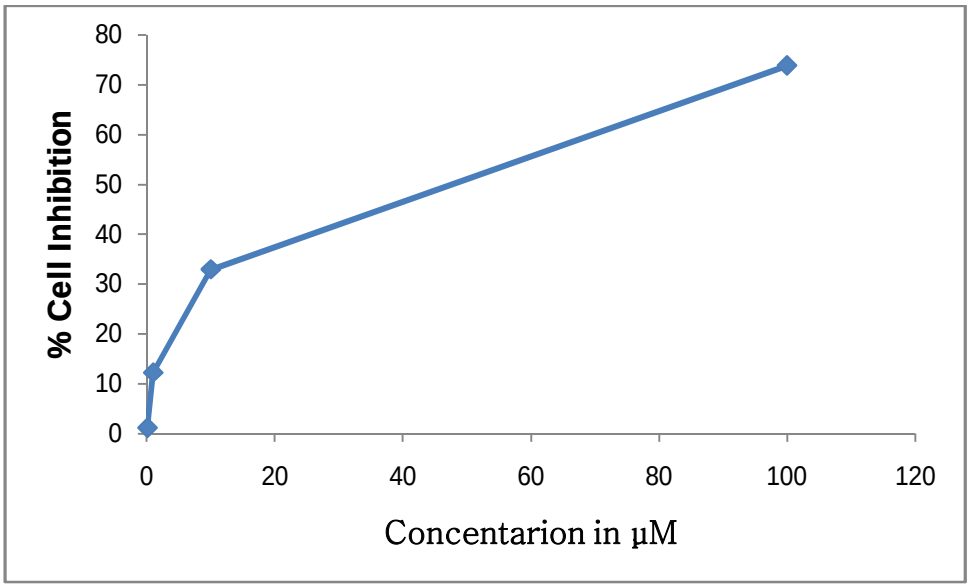


Table No.6 TD7

Concentration (µM)	%Growth Inhibition	IC_{50}	R^2
0.1µM	3.4112	>100	0.9907
1µM	13.7176		
10µM	33.8976		
100µM	74.8578		



CHAPTER– 5

RESULTS AND DISCUSSION

5.1. Chemical work:

The results of the present work are discussed under the following heads.

Scheme:2-(3-(4-(4-amino phenyl sulfonyl) phenyl)-4-oxo-2- (4-substituted-phenyl thiazolidin-5-yl) acetic acid.

5.1.1 Synthesis of 2-(3-(4-(4-aminophenylsulfonyl)phenyl)-4-oxo-2-(4-substituted-phenylthiazolidin-5-yl) acetic acid.

Synthetic route depicted in scheme outline the chemistry part of the presentwork. 2-(3-(4-(4-aminophenylsulfonyl)phenyl)-4-oxo-2-(4-substituted-phenylthiazolidin-5-yl) acetic acid **(TD1-7)** were obtained by the condensation of 4-(4-amino phenyl sulfonyl) benzenamine with substituted benzaldehydes in presence of dry dioxane, concentrated sulphuric acid and ethanol. The formation of the substituted thiazolidinone was confirmed by the presence of characteristic peaks in the IR spectra. It showed characteristic peaks at around 3400 cm^{-1} for NH_2 stretching and peak around 2900 cm^{-1} due to the presence of N=CH stretching. The NMR spectrum of the compounds TD1-7 showed the characteristic peak around δ 2.70 ppm for CH_3 group, δ 3.00 ppm for CH_2 and δ 5.70 ppm for NCH and also shows multiplet in the range of δ 6.80-8.30 ppm owing to aromatic protons. The appearance of peak due to chlorine in IR spectra around 700 -800 cm^{-1} and formation M+2 peak in the mass spectra. Data from the elemental analyses and molecular ion recorded in the mass spectra further confirmed the assigned structure.

5.2. Pharmacological Investigation

The anticancer screening of title compounds **(TD1-7)** were evaluated against human cervical cancer cell line (HeLa) by MTT assay method. In this assay the effective ranges of

anticancer activity for compounds **TD1-7** were in the concentration of 0.1, 1.0, 10, 100 µM respectively in the human cervical cancer cell line (HeLa). Triplicate was maintained and the medium containing without samples were served as control.

TD1 (*p*-nitrophenyl) produced IC_{50} value 45.70 µM in case of the human cervical cancer cell line (HeLa). Relatively less value of IC_{50} indicates the sample has more anticancer activity. The compounds **TD1** (*p*-nitro phenyl) had shown the percentage of cell inhibition was 74.85 against the human cervical cancer cell line (HeLa) in the highest concentration, which have *p*-nitrophenyl group in the thiazolidinone nucleus.

The result indicates that **TD1** (*p*-nitrophenylgroup) showed a significant anticancer activity against the human cervical cancer cell line (HeLa), when compared to that control.

TD2 (dimethyl amino group) produced IC_{50} value 66.23 µM in case of the human cervical cancer cell line (HeLa). Relatively less value of IC_{50} indicates the sample has more anticancer activity. The compound **TD2** (dimethyl amino group) had shown the percentage of cell inhibition was 52.89 against the human cervical cancer cell line (HeLa) in the highest concentration, which have dimethylamino group in the thiazolidinone nucleus.

The results indicate that **TD2** (dimethyl amino group) showed a moderate anticancer activity against the human cervical cancer cell line (HeLa), when compared to that of control.

TD3 (methoxyl group) produced IC_{50} value 75.26µM in case of the human cervical cancer cell line (HeLa). Relatively less value of IC_{50} indicates the sample has more anticancer activity. The compound **TD2** (methoxyl group) had shown the percentage of cell inhibition was 52.25 against the human cervical cancer cell line (HeLa), which have dimethyl amino group in the thiazolidinone nucleus.

The results indicate that **TD3** (methoxyl group) showed a less anticancer activity against the human cervical cancer cell line (HeLa), when compared to that of control.

TD4 (Hydroxyl group) produced IC_{50} value 92.36 μM in case of the human cervical cancer cell line (HeLa). Relatively less value of IC_{50} indicates the sample has more anticancer activity. The compound **TD4** (Hydroxyl group) had shown the percentage of cell inhibition was 63.82 against the human cervical cancer cell line (HeLa) in the highest concentration, which have imidazole group in the thiadiazole nucleus.

The results indicate that **TD4** (Hydroxyl group) showed a moderate significant anticancer activity against the human cervical cancer cell line (HeLa), when compared to that of control.

TD5 (vinyl group) produced IC_{50} value 75.26 μM in case of the human cervical cancer cell line (HeLa). Relatively less value of IC_{50} indicates the sample has more anticancer activity. The compound **TD5** (vinyl group) had shown the percentage of cell inhibition was 55.05 against the human cervical cancer cell line (HeLa) in the highest concentration, which have vinyl group in the thiazolidinone nucleus.

The results indicate that **TD5** (vinyl group) showed a moderate significant anticancer activity against the human cervical cancer cell line (HeLa), when compared to that of control.

TD6 (*p*-amino grp) producedIC_{50}value 48.60 μM in case of the human cervical cancer cell line (HeLa). Relatively high value of IC_{50} indicates the sample has more anticancer activity. The compound **TD6** (*p*-amino group) had shown the percentage of cell inhibition was 73.85 against the human cervical cancer cell line (HeLa) in the highest concentration, which have *p*-amino group in the thiazolidinone nucleus.

The results indicates that **TD6** (*p*-amino group) showed a good significant anticancer activity against the human cervical cancer cell line (HeLa), when compared to that of control.

TD7 (*p*-chloro group) produced IC_{50} value > 100 μM in case of the human cervical cancer cell line (HeLa). Relatively high value of IC_{50} indicates the sample has more and significant anticancer activity. The compound **TD7** (*p*-chloro group) had shown the percentage of cell inhibition was 55.05 against the human cervical cancer cell line (HeLa) in the highest concentration, which have *p*-chloro group in the thiadiazole nucleus.

The results indicates that **TD7** (*p*-chloro group) showed a more significant anticancer activity against the human cervical cancer cell line (HeLa), when compared to that of control.

The best mean IC_{50} values were achieved with compound (**TD3, TD4, TD5** and **TD7**) with slight difference among them. Title compounds (**TD1-7**) were found to exhibit mild to moderate anticancer activities in cell lines and the results were summarized below:

- Compound **TD1** (*p*-nitrophenyl group) shows less activity against the HeLa (IC_{50} – 47.50) cancer cell lines.
- Compound **TD2** (dimethylamino group) shows moderate activity against the HeLa (IC_{50} – 66.23) cancer cell lines.
- Compound **TD3** (methoxyl group) shows high significant activity against the HeLa (IC_{50} 72.56) cancer cell lines.
- Compound **TD4** (4-hydroxl group) shows more & potent significant against the HeLa (IC_{50} –92.36) cancer cell lines.
- Compound **TD5** (vinyl group) shows the moderate activity against the HeLa (IC_{50} – 68.25) cancer cell lines.

- Compound **TD6** (*p*-amino group) shows less significant activity against the HeLa (IC_{50} –48.60) cancer cell lines.
- Compound **TD7** (*p*-chloro) shows very high and potent significant activity against the HeLa (IC_{50} > 100) cancer cell lines.

Among the test compounds, compound 3-(4-(4-aminophenylsulfonyl)phenyl)-2-(4-chlorophenyl)-4-oxothiazolidin-5-yl) acetic acid (**TD7**) was found to be the most active agent which showed 74.85 percentage of cell inhibition against the human cervical cancer cell line (HeLa) in the highest concentration, which have *p*-chloro group in the thiazolidinone nucleus.

CHAPTER–6

SUMMARY AND CONCLUSION

In summary, a new series of 2-(3-(4-(4-aminophenylsulfonyl) phenyl)-4-oxo-2-(4-substituted-phenyl thiazolidin-5-yl) acetic acid were synthesized. These title compounds containing seven different substituents at C-2 and C-3 were screened for their anticancer agents. Most of the test compounds were found to exhibit significant anticancer activity against the human cervical cancer cell line (HeLa) in the highest concentration. Among the substituents at C-2, *p*-chloro phenyl substituent and at C-5 4-amino phenyl sulfonyl substitutent showed maximum potency, while 4-methoxy phenyl, 4- hydroxy phenyl and 4-nitro phenyl substitutent showed equipotent activity but the dimethylaminophenyl, vinyl and 4-amino phenyl substituent at C-2 exhibited least activity when compare to other substituents. The order of activity at C-2 is *p*-chloro phenyl ≥ 4- hydroxy phenyl ≥ 4-methoxy phenyl ≥ 4-nitro phenyl ≥ 4-amino phenyl ≥ dimethylaminophenyl ≥ vinyl substituents.

Among the test compounds, compound 3-(4-(4-aminophenylsulfonyl)phenyl)-2-(4-chlorophenyl)-4-oxothiazolidin-5-yl) acetic acid (**TD7**) was found to be the most active agent which showed 74.85 percentage of cell inhibition against the human cervical cancer cell line (HeLa) in the highest concentration, which have *p*-chlorophenyl group in the thiazolidinone nucleus.

Hence this molecule can be selected as a lead molecule of the present study for further exploitation.

CHAPTER- 7

FUTURE PLAN OF WORK

It may conclude that further beneficial pharmacophore modifications in the design of novel 2, 3-disubstituted thiazolidinone derivatives may be synthesized by designing novel ligands for therapeutic target by substituting different functional group and also examine with the help of NMR and X-ray which provide three dimensional frame works which can analyze structure activity data and can guide the design and synthesis of future potential therapeutic drugs towards other chronic disorders.

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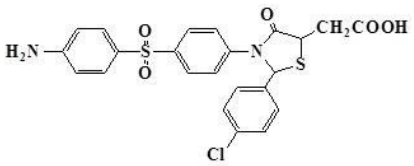
Compound Name: TD7



BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

Current Data Parameters	
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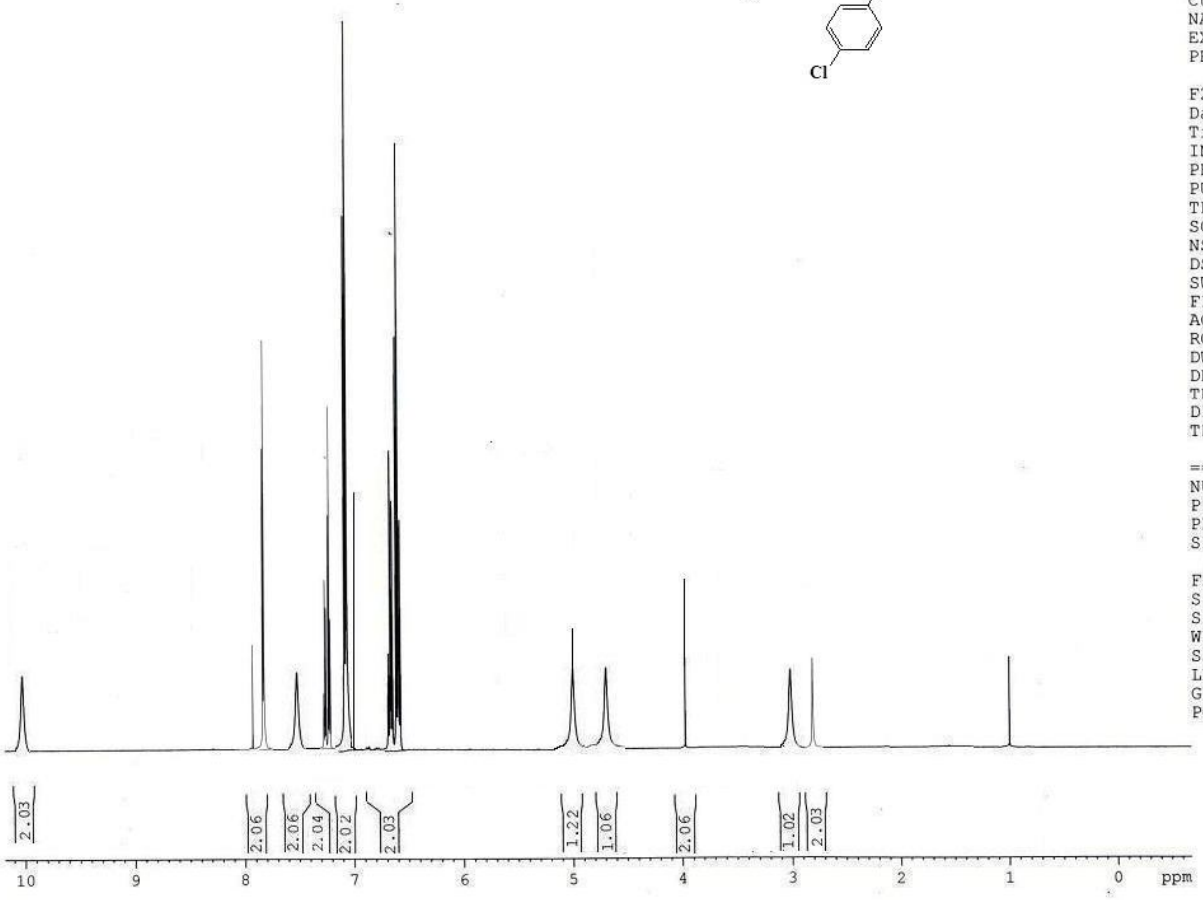
EXPNO	361
PROCNO	1

F2 - Acquisition Parameters	
Date_	20100626
Time	12.40
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	16
DS	2
SWH	12019.230 Hz
FIDRES	0.183399 Hz
AQ	2.7263477 sec
RG	362
DW	41.600 usec
DE	6.00 usec
TE	296.3 K
D1	1.00000000 sec
TD0	1

======== CHANNEL f1 ========	
NUC1	1H
P1	10.90 usec
PL1	-3.00 dB
SFO1	400.1324008 MHz

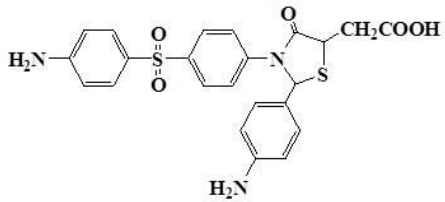
F2 - Processing parameters	
SI	32768
SF	400.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

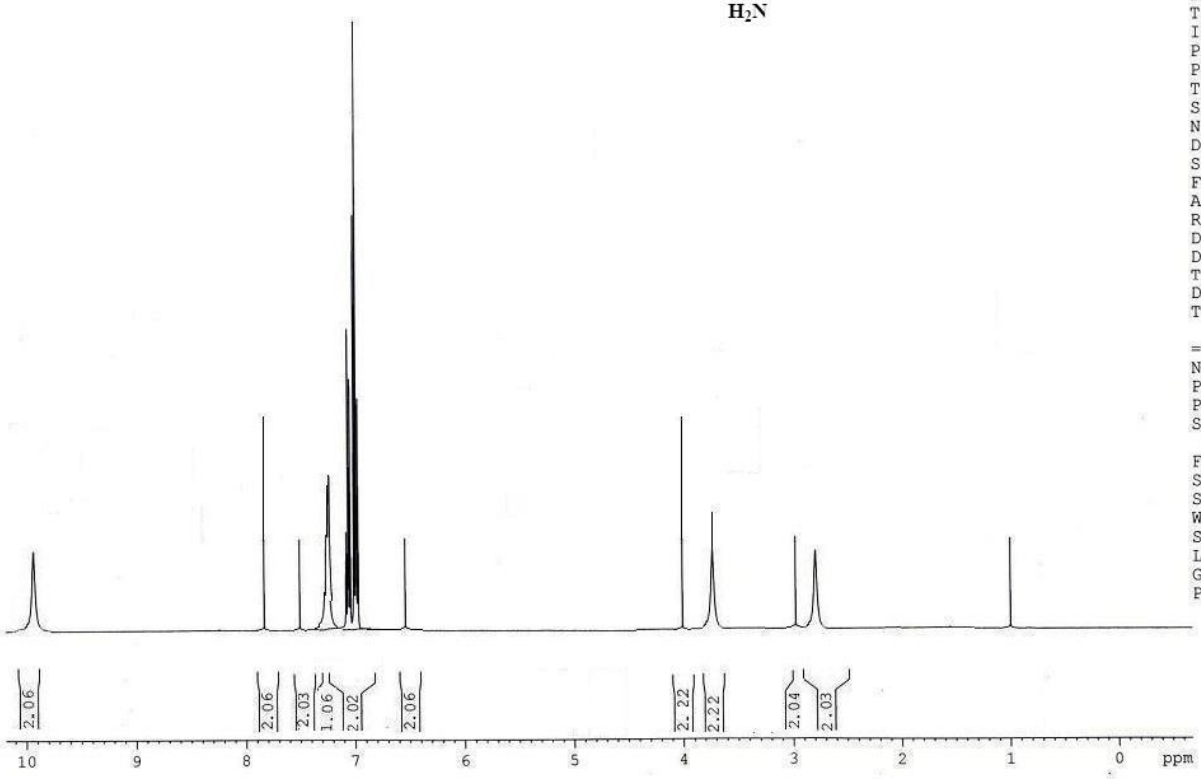


(3-(4-(4-aminophenylsulfonyl)phenyl)-2-(4-chlorophenyl)-4-oxothiazolidin-5-yl)acetic acid (TD 7).

avtar_saifpu@yahoo.co.in

Compound Name: TD6





BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

Current Data Parameters	
NAME	Jun26-2017
EXPNO	361
PROCNO	1

F2 - Acquisition Parameters	
Date_	20100626
Time	12.40
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	16
DS	2
SWH	12019.230 Hz
FIDRES	0.183399 Hz
AQ	2.7263477 sec
RG	362
DW	41.600 usec
DE	6.00 usec
TE	296.3 K
D1	1.00000000 sec
TD0	1

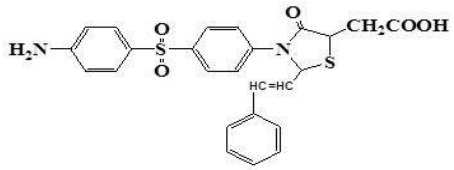
======== CHANNEL f1 ========	
NUC1	1H
P1	10.90 usec
PL1	-3.00 dB
SFO1	400.1324008 MHz

F2 - Processing parameters	
SI	32768
SF	400.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

(3-(4-(4-aminophenylsulfonyl)phenyl)-2-(4-aminophenyl)-4-oxothiazolidin-5-yl)aceticacid (TD 6).

avtar_saifpu@yahoo.co.in

Compound Name: T D5



(3-(4-(4-aminophenylsulfonyl)phenyl)-4-oxo-2-styrylthiazolidin-5-yl)acetic acid (TD 5).

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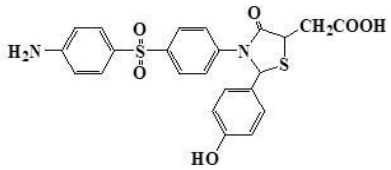
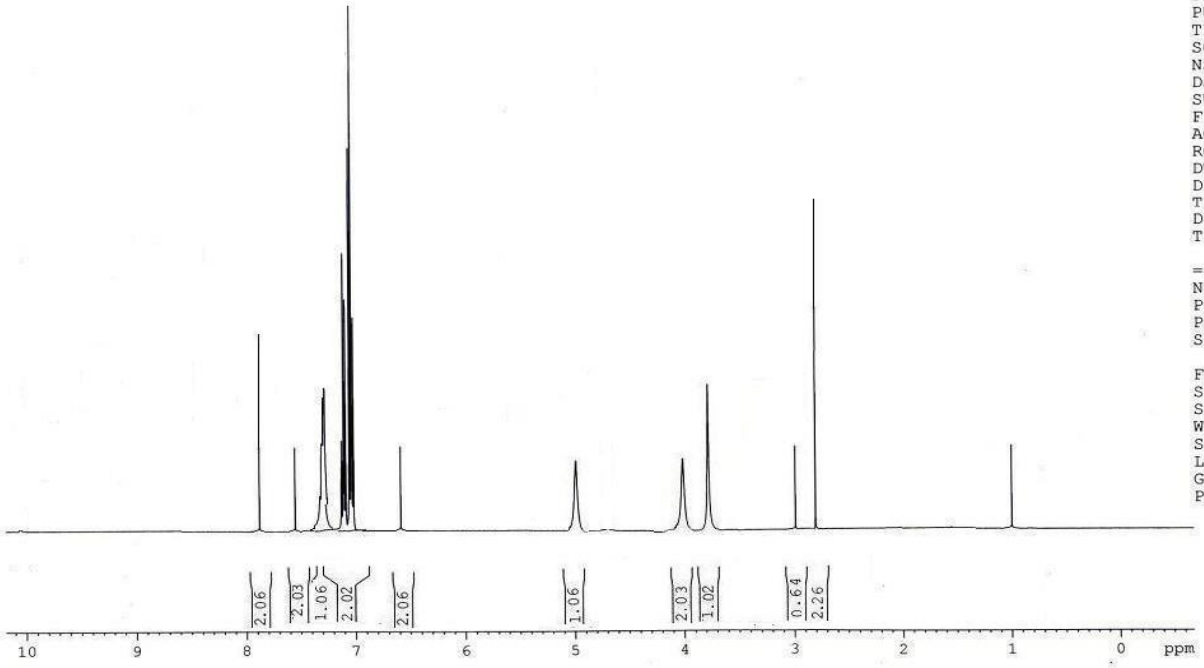
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

Current Data Parameters	
NAME	Jun25-2017
EXPNO	362
PROCNO	1
F2 - Acquisition Parameters	
Date_	20100626
Time	13.20
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	16
DS	2
SWH	12019.230 Hz
FIDRES	0.183399 Hz
AQ	2.7263477 sec
RG	362
DW	41.600 usec
DE	6.00 usec
TE	296.3 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	10.90 usec
PL1	-3.00 dB
SFO1	400.1324008 MHz
F2 - Processing parameters	
SI	32768
SF	400.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

avtar_saifpu@yahoo.co.in

Compound Name: TD4





BRUKER
AVANCE II 400 NMR
Spectrometer
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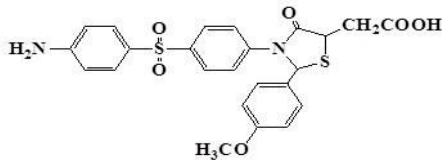
Panjab University
Chandigarh

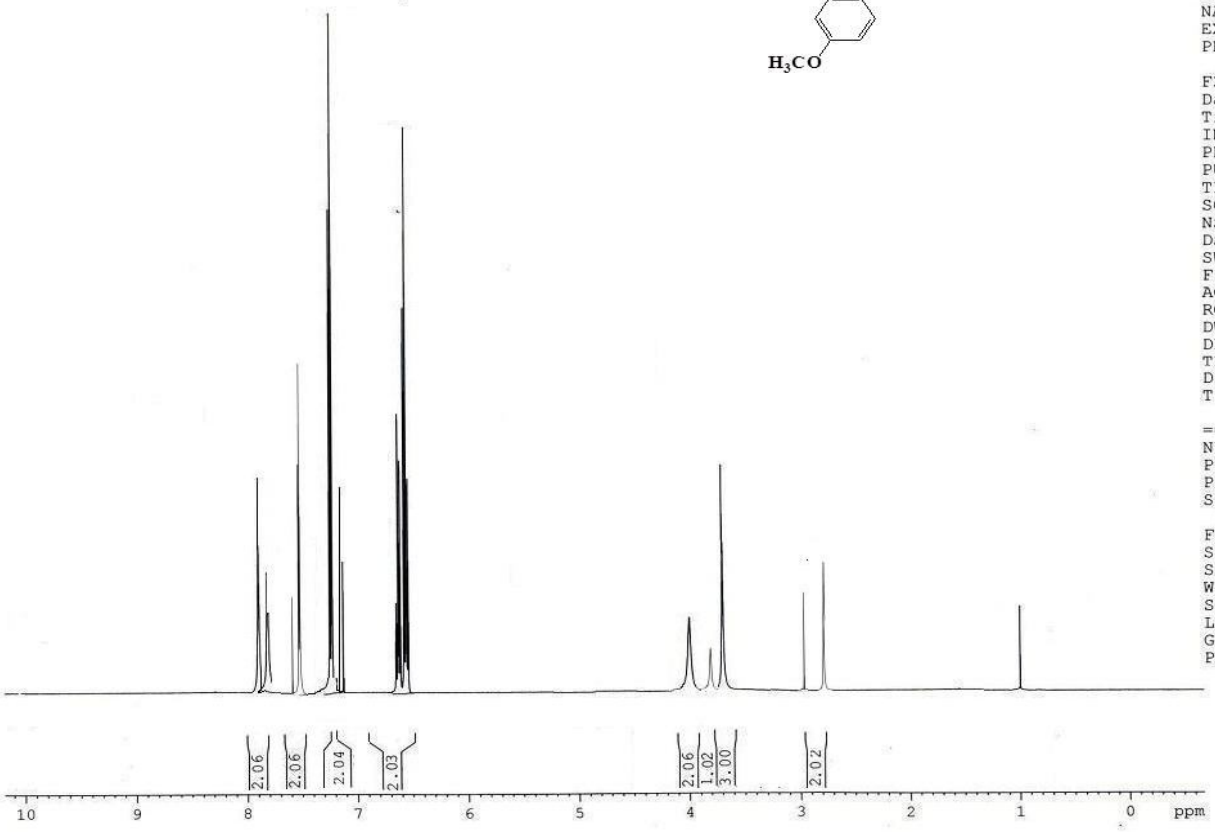
Current Data Parameters	
NAME	Jun25-2017
EXPNO	361
PROCNO	1
F2 - Acquisition Parameters	
Date_	20100626
Time	12.40
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	16
DS	2
SWH	12019.230 Hz
FIDRES	0.183399 Hz
AQ	2.7263477 sec
RG	362
DW	41.600 usec
DE	6.00 usec
TE	296.3 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	10.90 usec
PL1	-3.00 dB
SFO1	400.1324008 MHz
F2 - Processing parameters	
SI	32768
SF	400.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

(3-(4-(4-aminophenylsulfonyl) phenyl)-2-(4-hydroxyphenyl)-4-oxothiazolidin-5-yl)acetic acid (TD 4).

avtar_saifpu@yahoo.co.in

Compound Name: TD3





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AVANCE II 400 NMR
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Current Data Parameters	
NAME	Jun25-2017
EXPNO	360
PROCNO	1

F2 - Acquisition Parameters	
Date_	20100626
Time	14.40
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	16
DS	2
SWH	12019.230 Hz
FIDRES	0.183399 Hz
AQ	2.7263477 sec
RG	362
DW	41.600 usec
DE	6.00 usec
TE	296.3 K
D1	1.00000000 sec
TD0	1

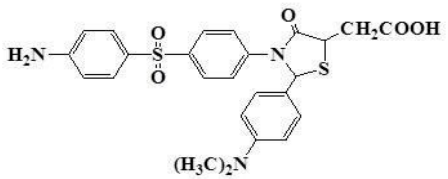
======== CHANNEL f1 ========	
NUC1	1H
P1	10.90 usec
PL1	-3.00 dB
SFO1	400.1324008 MHz

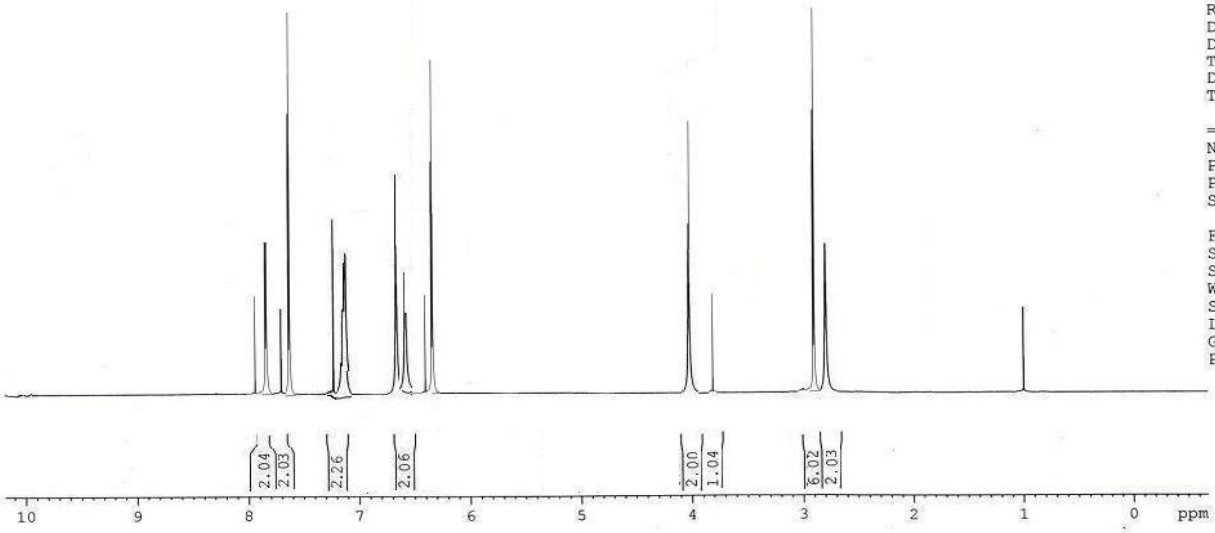
F2 - Processing parameters	
SI	32768
SF	400.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

3-(4-(4-aminophenylsulfonyl)phenyl)-2-(4-methoxyphenyl)-4-oxothiazolidin-5-yl)acetic acid (TD 3).

avtar_saifpu@yahoo.co.in

Compound Name: TD2





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AVANCE II 400 NMR
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Current Data Parameters	
NAME	Jun25-2017
EXPNO	359
PROCNO	1

F2 - Acquisition Parameters	
Date_	20100626
Time	13.40
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	16
DS	2
SWH	12019.230 Hz
FIDRES	0.183399 Hz
AQ	2.7263477 sec
RG	362
DW	41.600 usec
DE	6.00 usec
TE	296.3 K
D1	1.00000000 sec
TD0	1

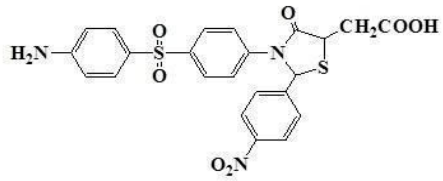
======== CHANNEL f1 ========	
NUC1	1H
P1	10.90 usec
PL1	-3.00 dB
SFO1	400.1324008 MHz

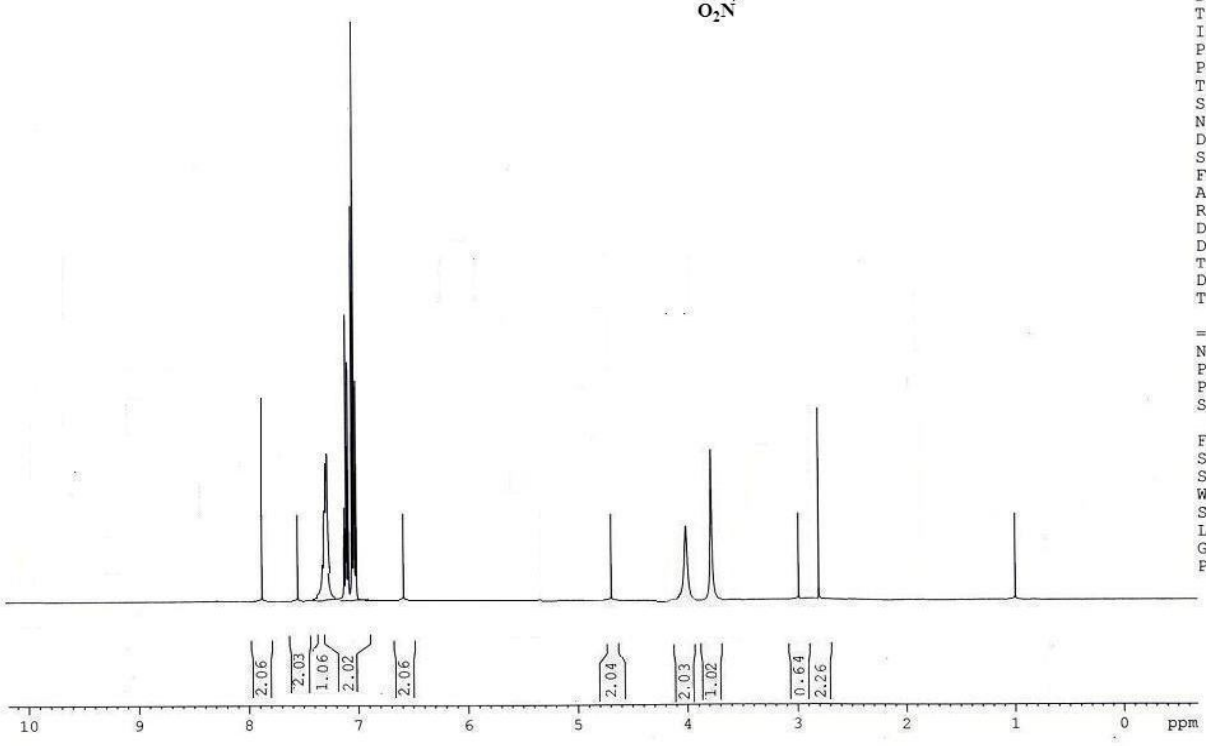
F2 - Processing parameters	
SI	32768
SF	400.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

3-(4-(4-aminophenylsulfonyl)phenyl)-2-(4-(dimethylamino)phenyl)-4-oxothiazolidin-5-yl)acetic acid (TD2)

avtar_saifpu@yahoo.co.in

Compound name : TD1





3-(4-(4-aminophenylsulfonyl) phenyl)-2-(2-nitrophenyl)-4-oxothiazolidin-5-yl) acetic acid (TD1)

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Panjab University
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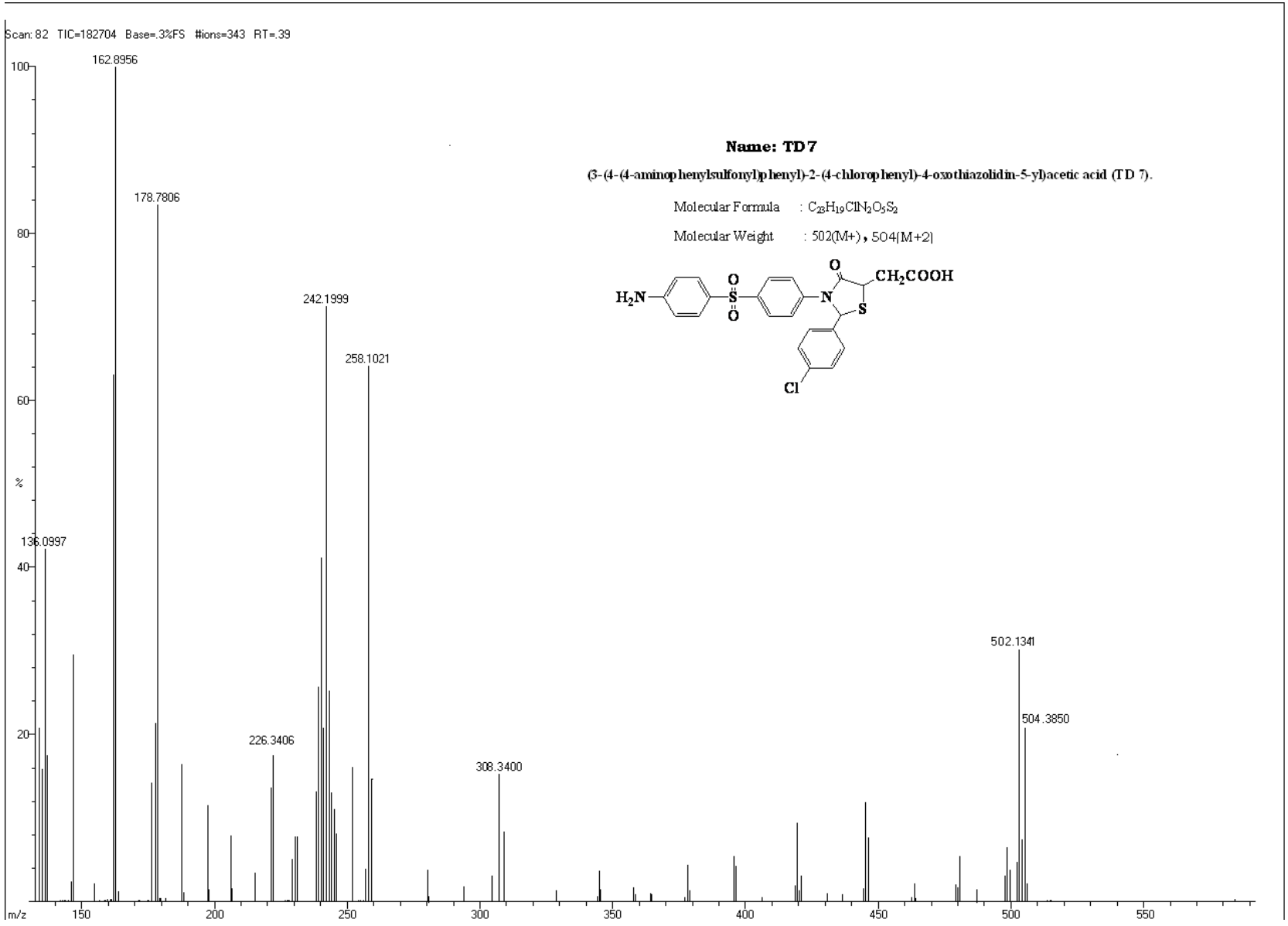
Current Data Parameters	
NAME	Jun25-2017
EXPNO	359
PROCNO	1

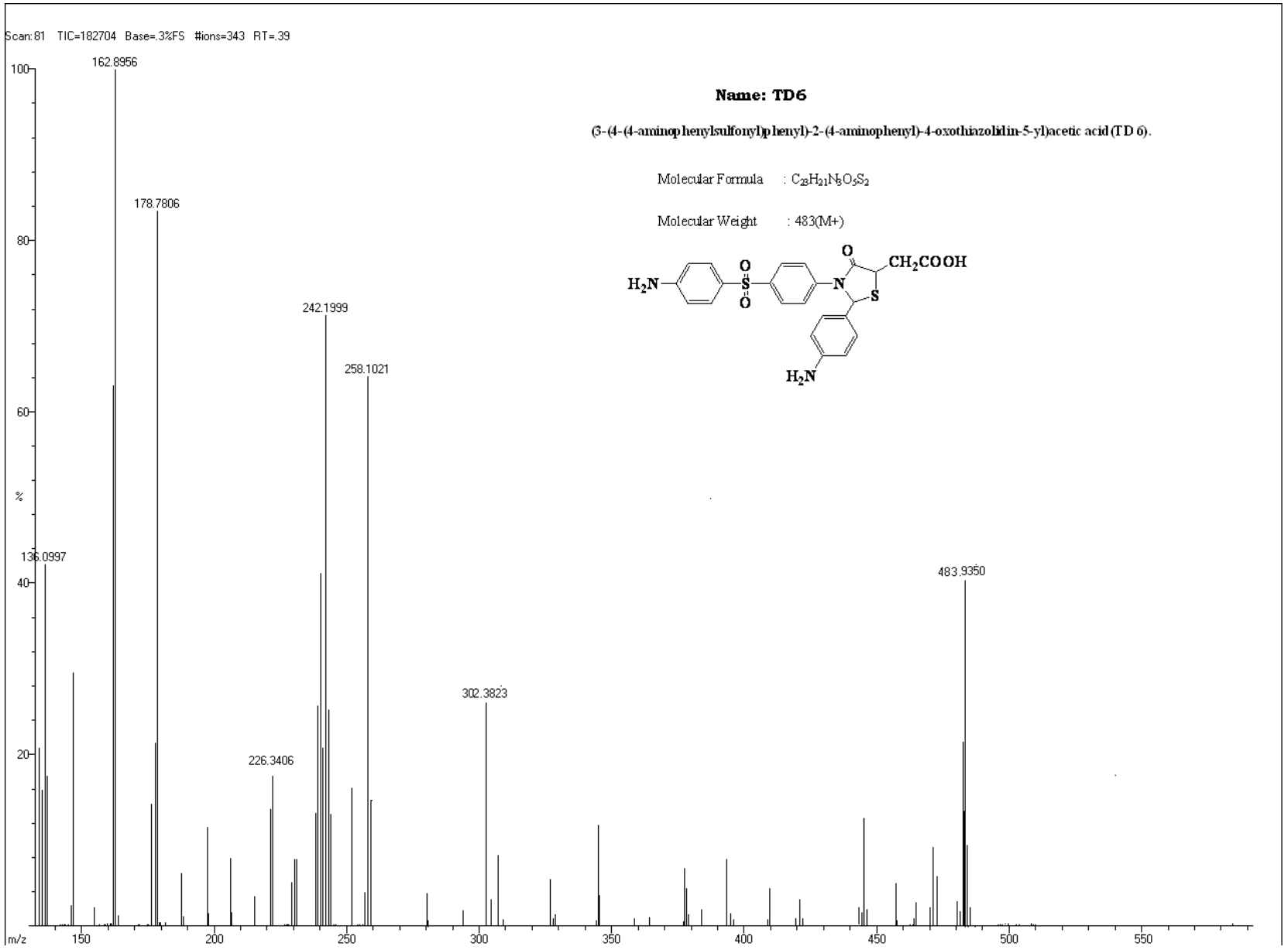
F2 - Acquisition Parameters	
Date_	20100626
Time	13.40
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	DMSO
NS	16
DS	2
SWH	12019.230 Hz
FIDRES	0.183399 Hz
AQ	2.7263477 sec
RG	362
DW	41.600 usec
DE	6.00 usec
TE	296.3 K
D1	1.00000000 sec
TD0	1

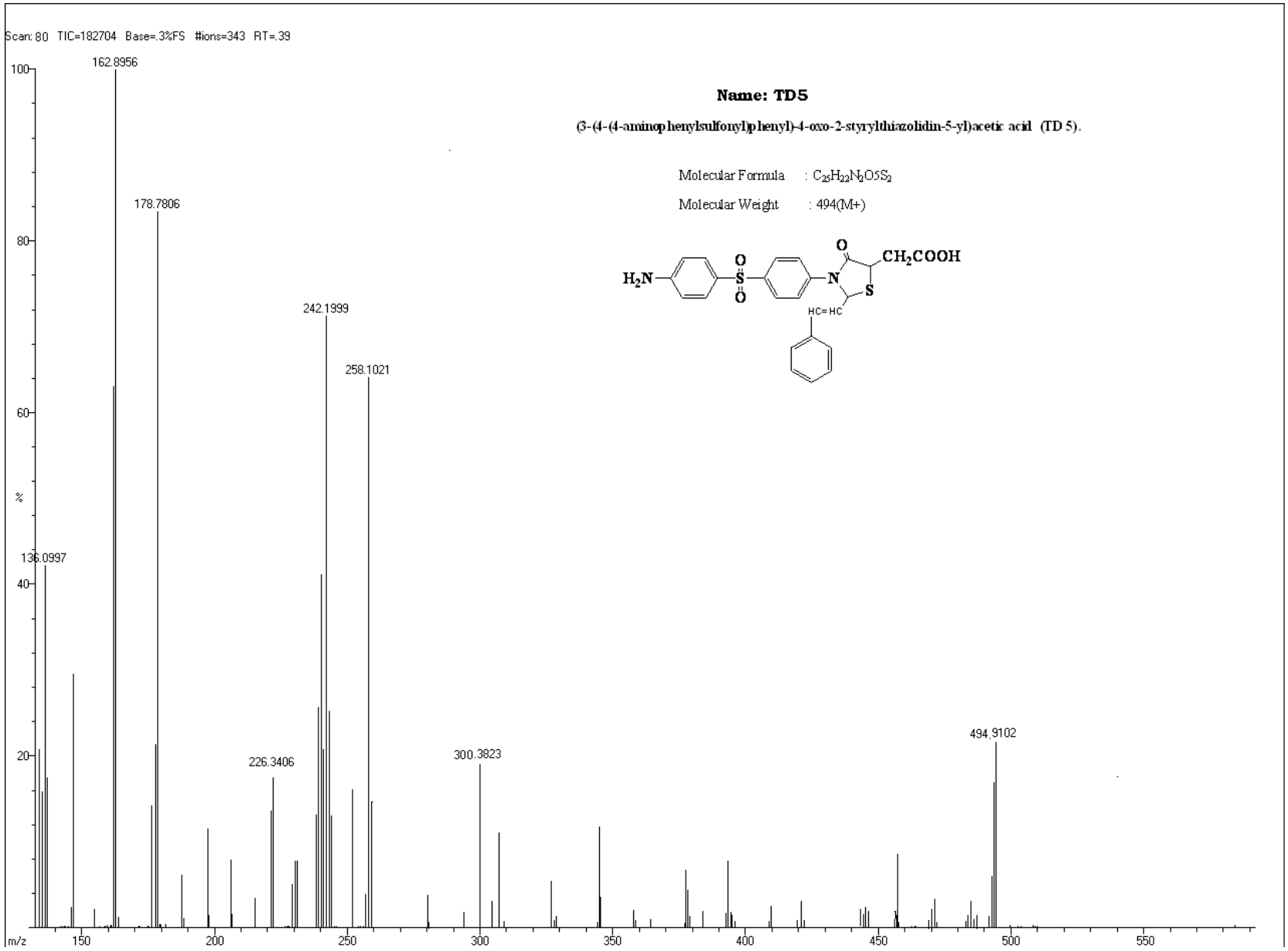
======== CHANNEL f1 ========	
NUC1	1H
P1	10.90 usec
PL1	-3.00 dB
SFO1	400.1324008 MHz

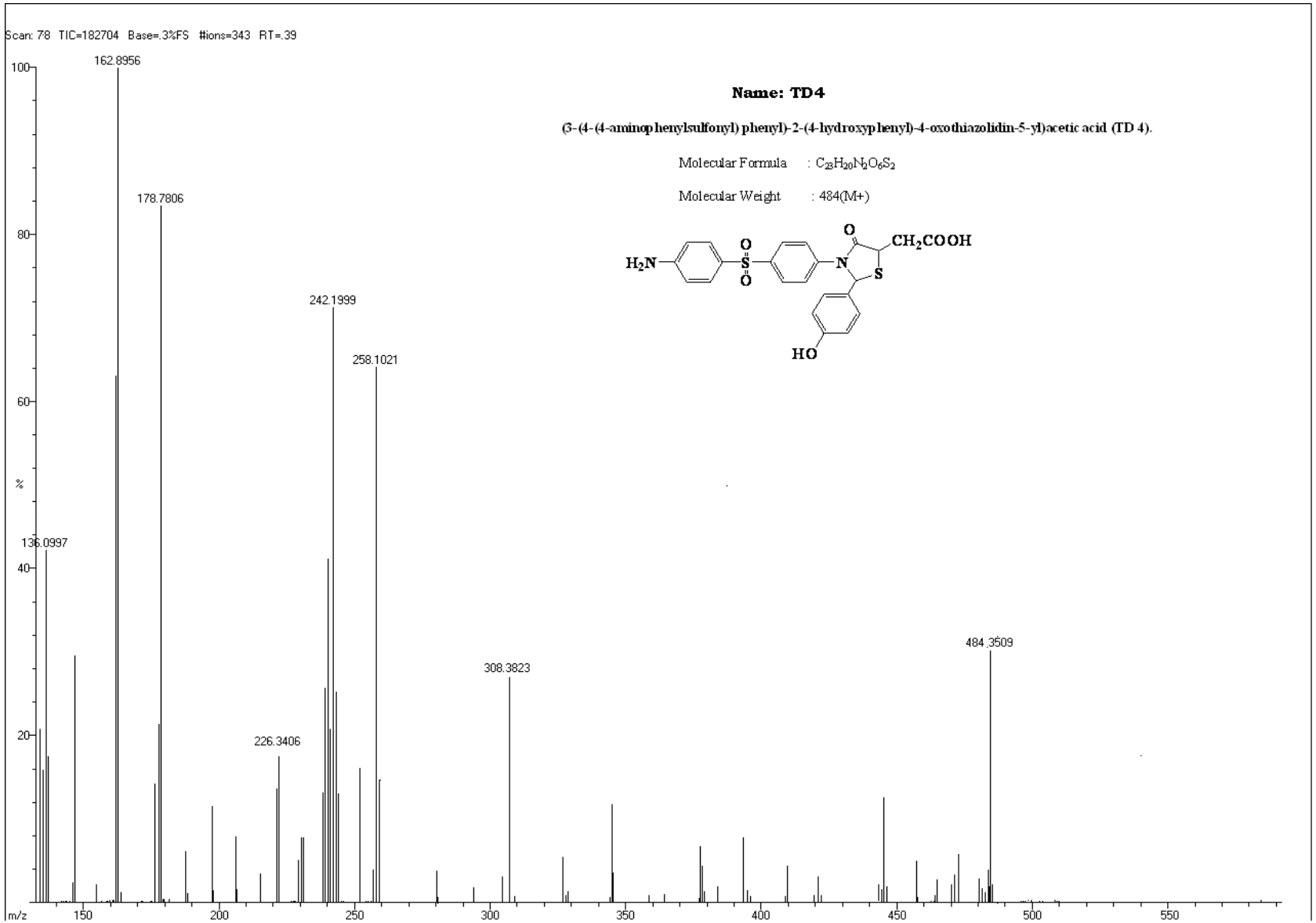
F2 - Processing parameters	
SI	32768
SF	400.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

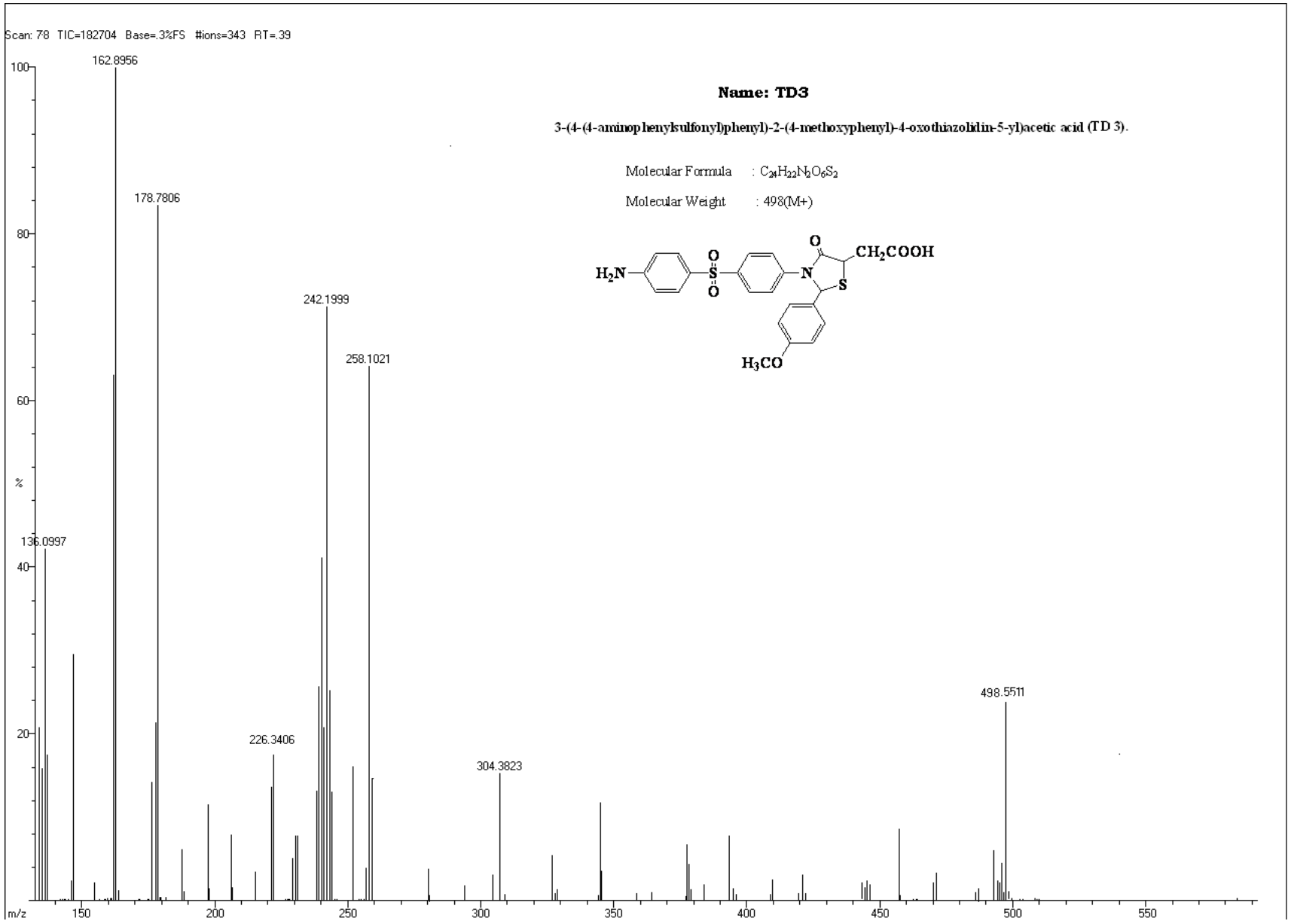
avtar_saifpu@yahoo.co.in

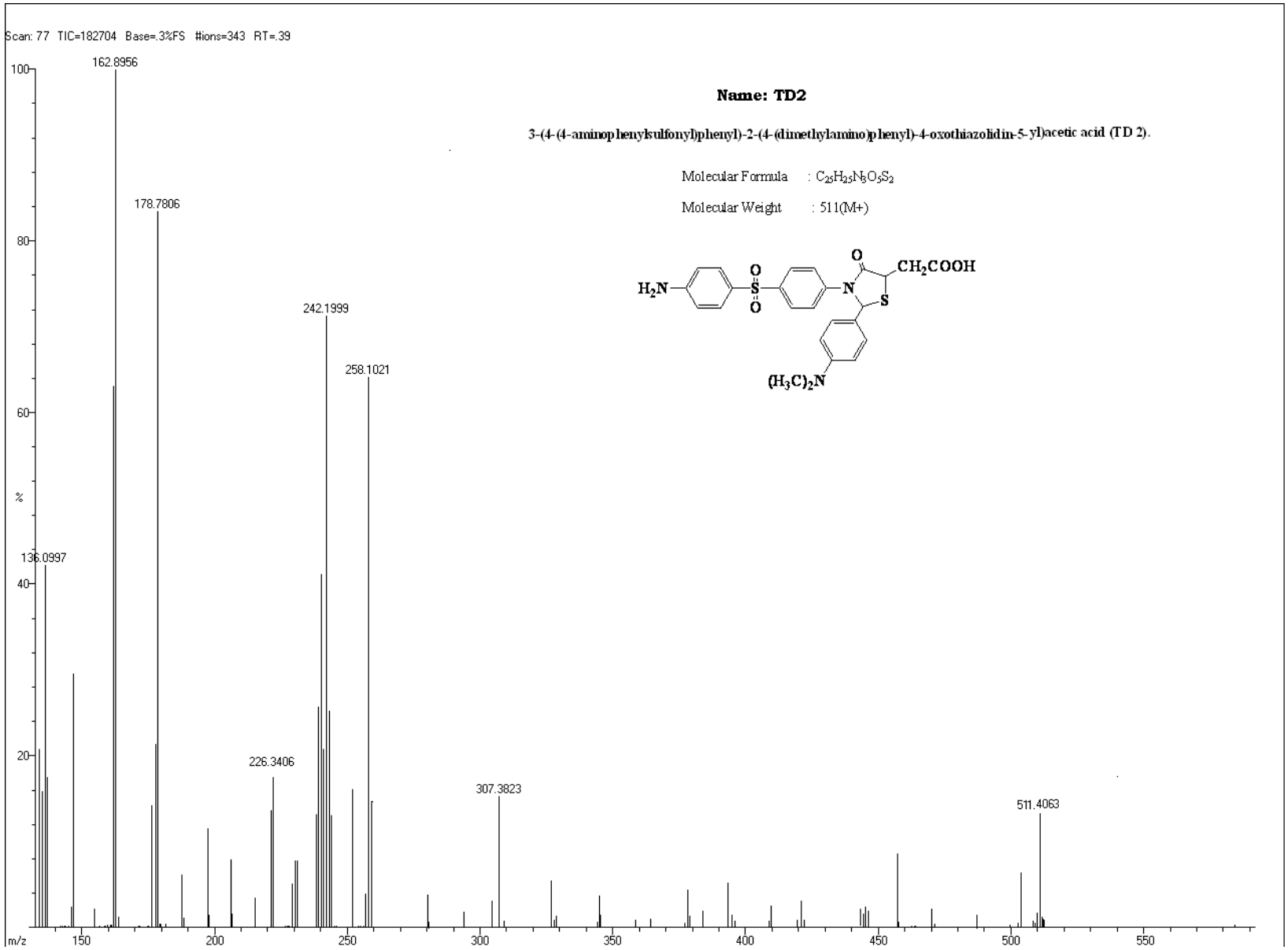

Scan: 82 TIC=182704 Base=.3%FS #ions=343 RT=.39
100
80
60
40
20
%
m/z
150
200
250
300
350
400
450
500
550
162.8956
178.7806
242.1999
258.1021
136.0997
226.3406
308.3400
502.1341
504.3850
Name: TD7
(3-(4-(4-aminophenylsulfonyl)phenyl)-2-(4-chlorophenyl)-4-oxothiazolidin-5-yl)acetic acid (TD 7).
Molecular Formula : C23H19ClN2O5S2
Molecular Weight : 502(M+), 504(M+2)
H2N
O
S
O
N
O
CH2COOH
S
Cl

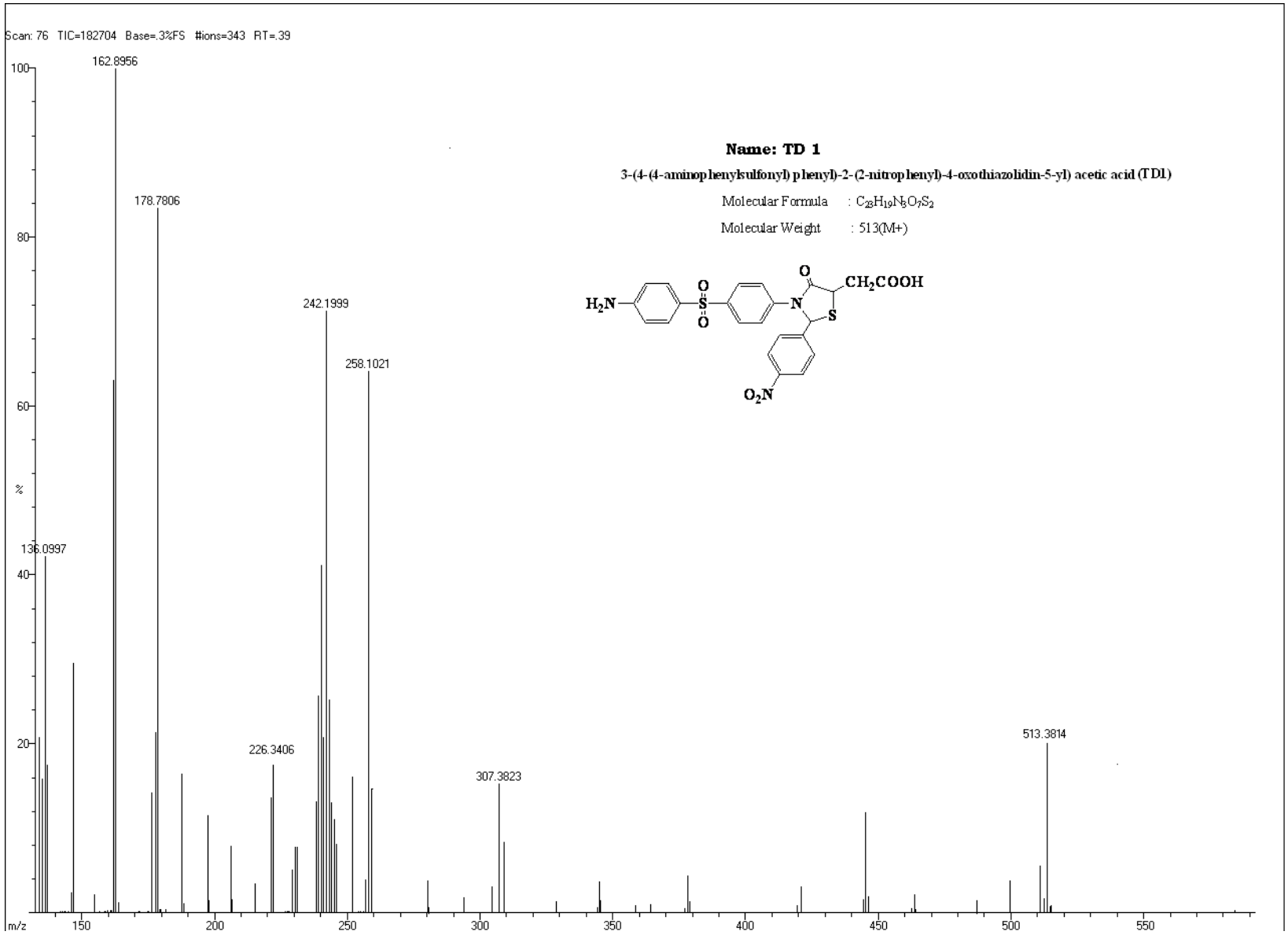

Scan:81 TIC=182704 Base=.3%FS #ions=343 RT=.39
Name: TD6
(3-(4-(4-aminophenylsulfonyl)phenyl)-2-(4-aminophenyl)-4-oxothiazolidin-5-yl)acetic acid (TD 6).
Molecular Formula : C28H21N3O5S2
Molecular Weight : 483(M+)
H2N
O
S
O
N
O
CH2COOH
S
H2N
162.8956
178.7806
242.1999
258.1021
136.0997
483.9350
302.3823
226.3406
100
80
60
40
20
%
m/z
150
200
250
300
350
400
450
500
550


Scan: 80 TIC=182704 Base=.3%FS #ions=343 RT=.39
Name: TD5
(3-(4-(4-aminophenylsulfonyl)phenyl)-4-oxo-2-styrylthiazolidin-5-yl)acetic acid (TD 5).
Molecular Formula : C25H22N2O5S2
Molecular Weight : 494(M+)
H2N
O
S
O
N
O
CH2COOH
S
HC=HC
162.8956
178.7806
242.1999
258.1021
136.0997
226.3406
300.3823
494.9102
100
80
60
40
20
%
m/z
150
200
250
300
350
400
450
500
550


Scan: 78 TIC=182704 Base=.3%FS #ions=343 RT=.39
Name: TD4
(3-(4-(4-aminophenylsulfonyl) phenyl)-2-(4-hydroxyphenyl)-4-oxothiazolidin-5-yl)acetic acid (TD 4).
Molecular Formula : C23H20N2O6S2
Molecular Weight : 484(M+)
H2N
O
S
O
N
O
CH2COOH
S
HO
162.8956
178.7806
242.1999
258.1021
136.0997
308.3823
226.3406
484.3509
100
80
60
40
20
%
m/z
150
200
250
300
350
400
450
500
550


Scan: 78 TIC=182704 Base=.3%FS #ions=343 RT=.39
Name: TD3
3-(4-(4-aminophenylsulfonyl)phenyl)-2-(4-methoxyphenyl)-4-oxothiazolidin-5-yl)acetic acid (TD 3).
Molecular Formula : C24H22N2O6S2
Molecular Weight : 498(M+)
H2N
O
S
O
N
O
CH2COOH
S
H3CO
162.8956
178.7806
242.1999
258.1021
136.0997
226.3406
304.3823
498.5511
100
80
60
40
20
%
m/z
150
200
250
300
350
400
450
500
550


Scan: 77 TIC=182704 Base=.3%FS #ions=343 RT=.39
Name: TD2
3-(4-(4-aminophenylsulfonyl)phenyl)-2-(4-(dimethylamino)phenyl)-4-oxothiazolidin-5-yl)acetic acid (TD 2).
Molecular Formula : C25H25N3O5S2
Molecular Weight : 511(M+)
H2N
O
S
O
N
O
CH2COOH
S
(H3C)2N
162.8956
178.7806
242.1999
258.1021
136.0997
226.3406
307.3823
511.4063
100
80
60
40
20
%
m/z
150
200
250
300
350
400
450
500
550


Scan: 76 TIC=182704 Base=.3%FS #ions=343 RT=.39
100
80
60
40
20
%
m/z
150
200
250
300
350
400
450
500
550
162.8956
178.7806
242.1999
258.1021
136.0997
226.3406
307.3823
513.3814
Name: TD 1
3-(4-(4-aminophenylsulfonyl) phenyl)-2-(2-nitrophenyl)-4-oxothiazolidin-5-yl) acetic acid (TD1)
Molecular Formula : C25H19N3O7S2
Molecular Weight : 513(M+)
H2N
O
S
O
N
O
CH2COOH
S
O2N

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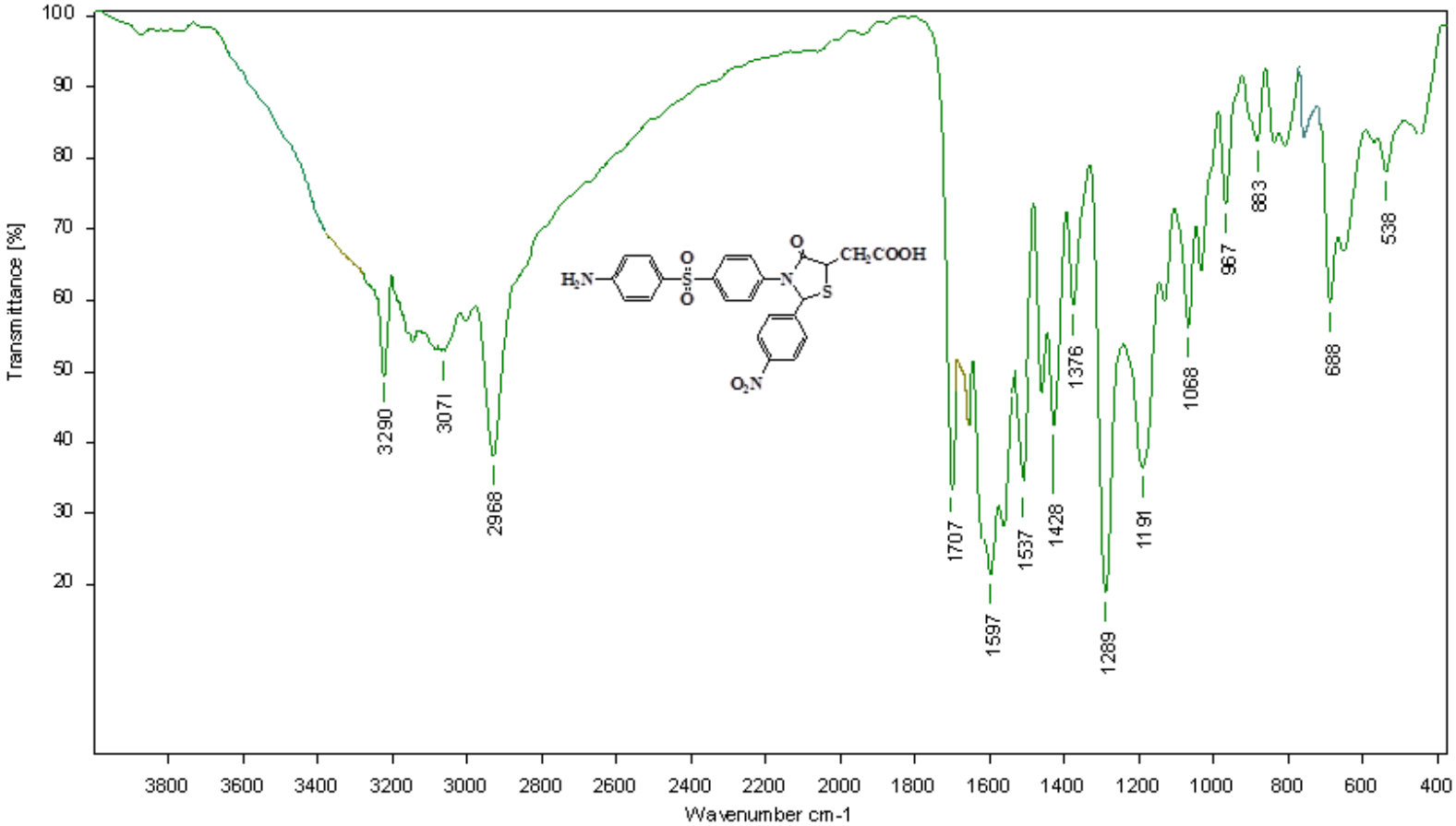
Kumarapalayam

4/26/2017 3:15:26 PM

Compound Name: TD1



3-(4-(4-aminophenylsulfonyl) phenyl)-2-(2-nitrophenyl)-4-oxothiazolidin-5-yl) acetic acid (TD1)

Experiment TRANS.xpm

Path of File C:\Program Files\OPUS_65\MEAS

Operator Name Administrator

Date of Measurement 26/04/2017

Instrument Type Alpha

Sample Form solid

Resolution 4

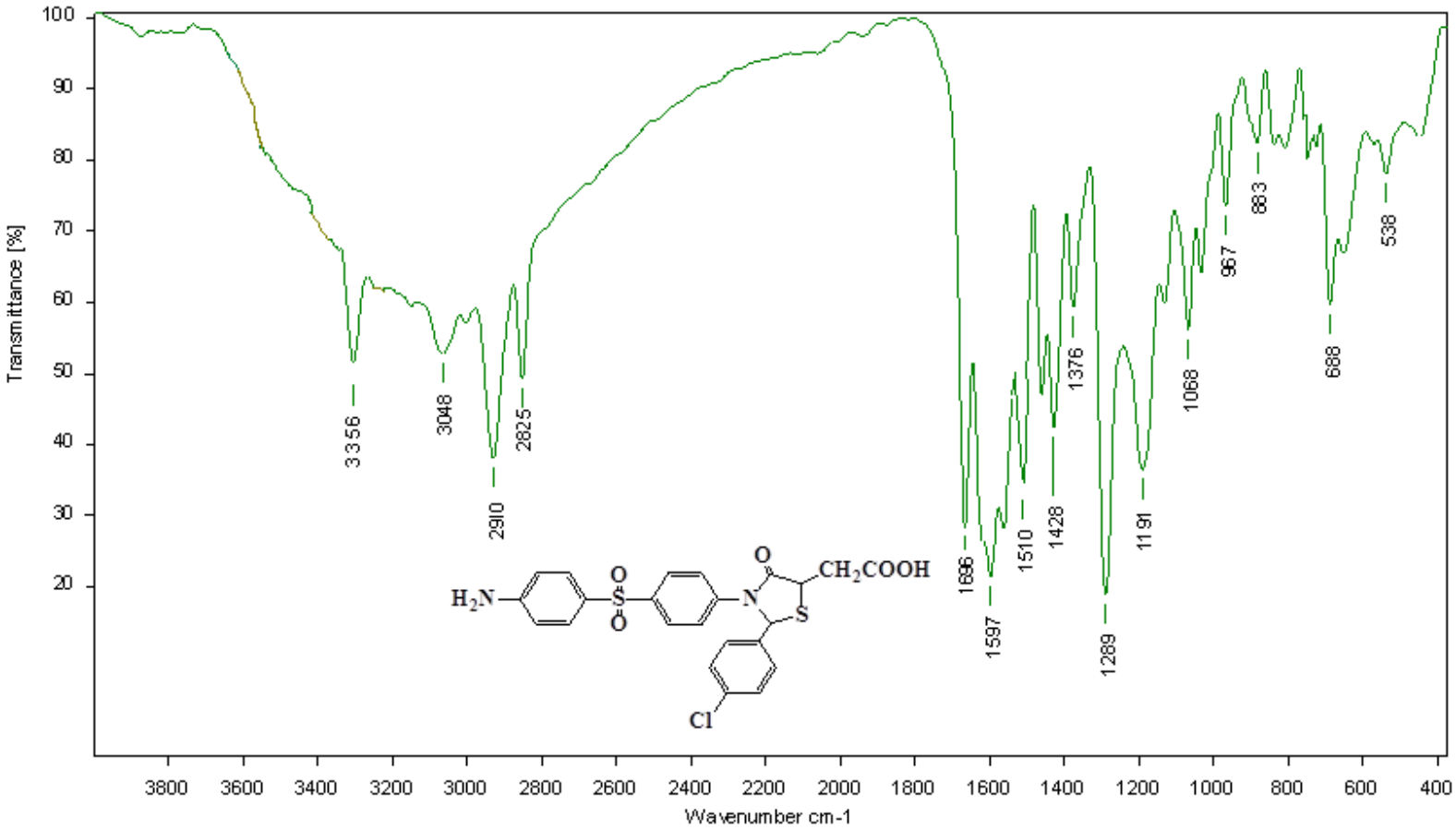
Sample Scans 16

Analyst name: Jayaseelan

JKK Nataraja College of Pharmacy
Kumarapalayam

3/16/2017 3:20:26 PM

Compound Name: TD7



(3-(4-(4-aminophenylsulfonyl)phenyl)-2-(4-chlorophenyl)-4-oxothiazolidin-5-yl)acetic acid (TD 7).

Experiment TRANS.xpm

Path of File C:\Program Files\OPUS_65\MEAS

Operator Name Administrator

Date of Measurement 16/03/1/2017

Instrument Type Alpha

Sample Form solid

Resolution 4

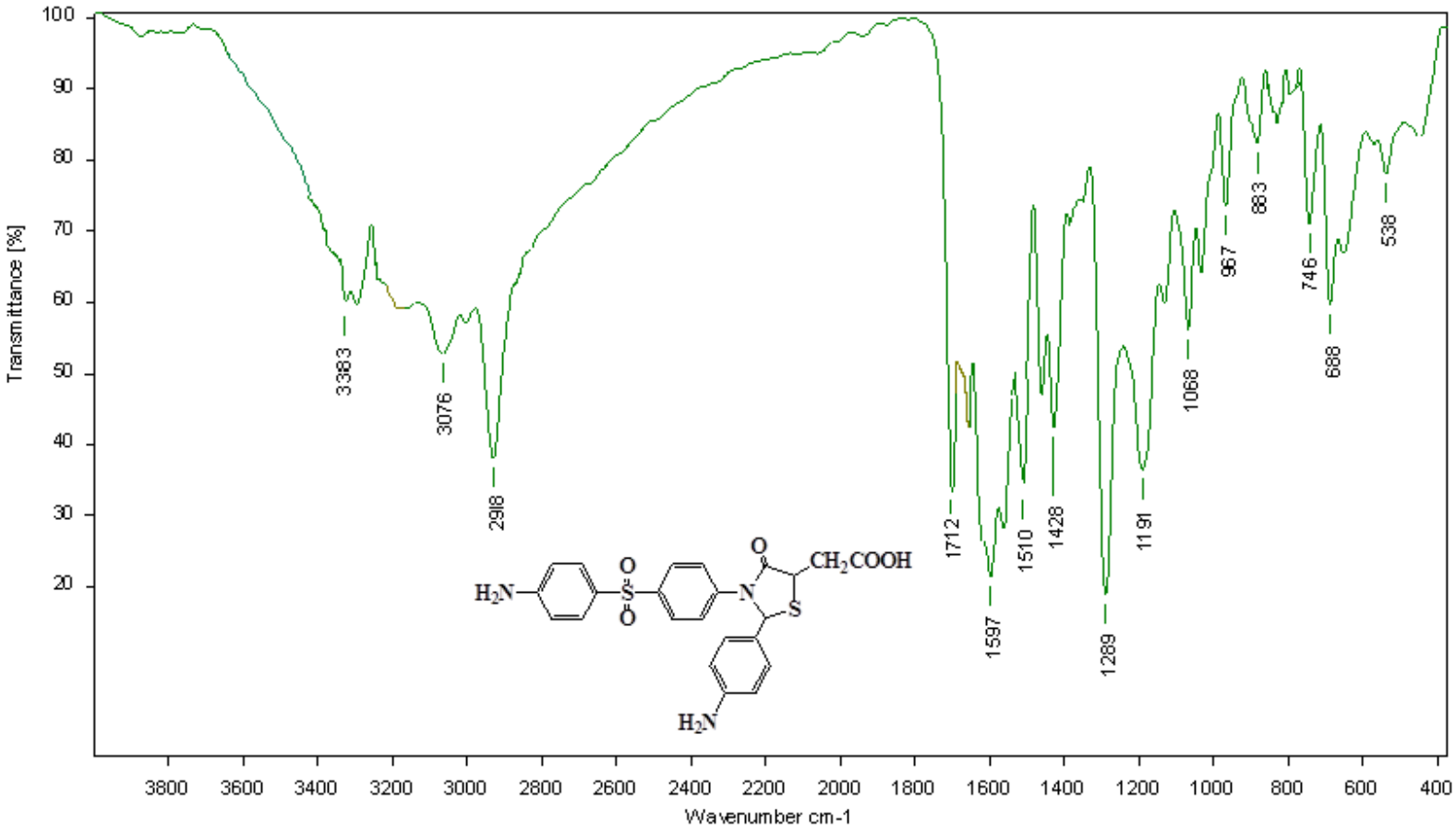
Sample Scans 16

Analyst name: Jayaseelan

JKK Nataraja College of Pharmacy
Kumarapalayam

6/28/2015 2:15:26 PM

Compound Name: TD6



(3-(4-(4-aminophenylsulfonyl)phenyl)-2-(4-aminophenyl)-4-oxothiazolidin-5-yl)acetic acid (TD 6).

Experiment TRANS.xpm

Path of File C:\Program Files\OPUS_65\MEAS

Operator Name Administrator

Date of Measurement 28/06/2015

Instrument Type Alpha

Sample Form solid

Resolution 4

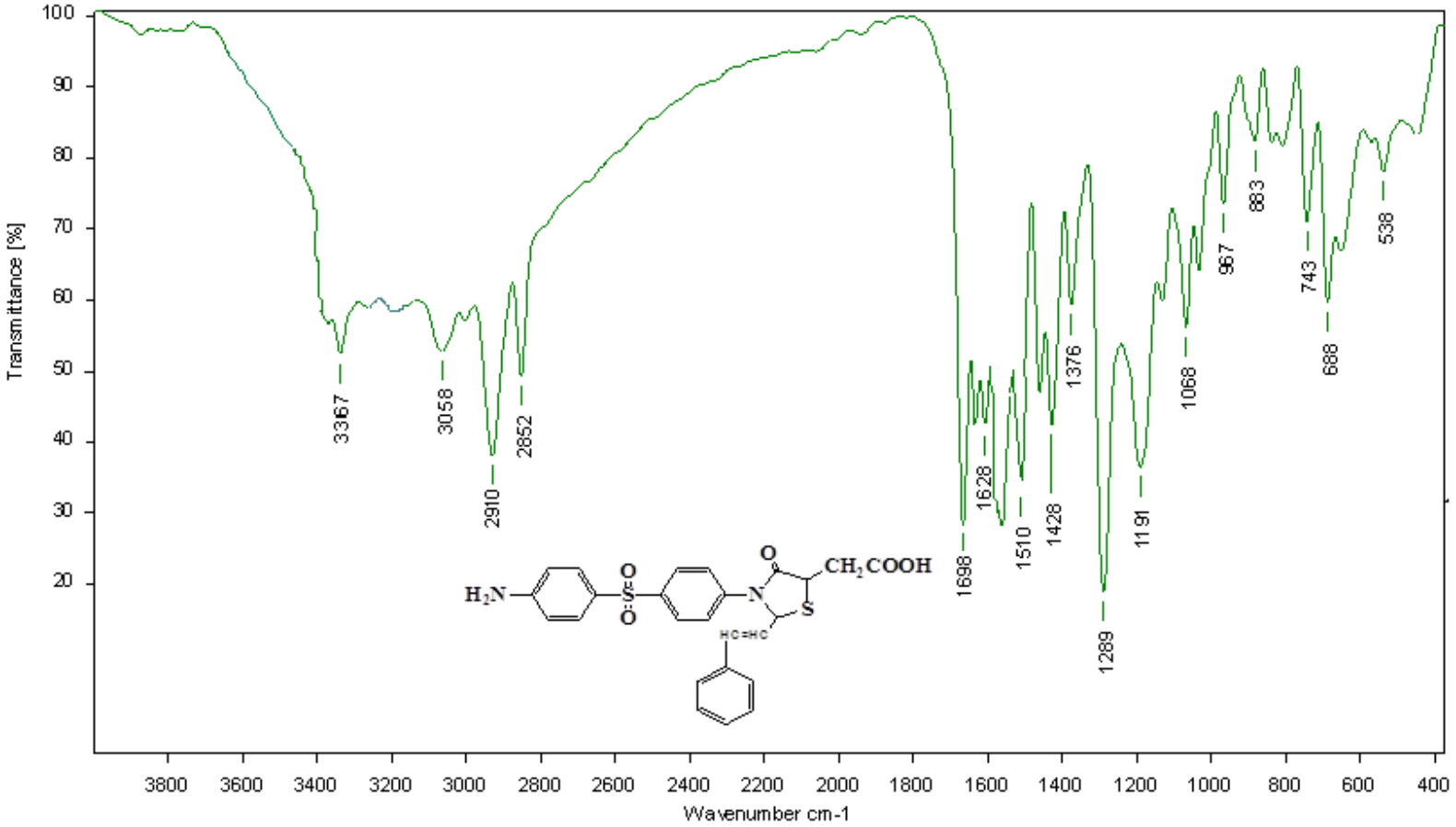
Sample Scans 16

Analyst name: Jayaseelan

JKK Nataraja College of Pharmacy
Kumarapalayam

3/16/2017 2:40:13 PM

Compound Name: TD5



(3-(4-(4-aminophenylsulfonyl)phenyl)-4-oxo-2-styrylthiazolidin-5-yl)acetic acid (TD 5).

Experiment TRANS.xpm

Path of File C:\Program Files\OPUS_65\MEAS

Operator Name Administrator

Date of Measurement 16/03/2017

Instrument Type Alpha

Sample Form solid

Resolution 4

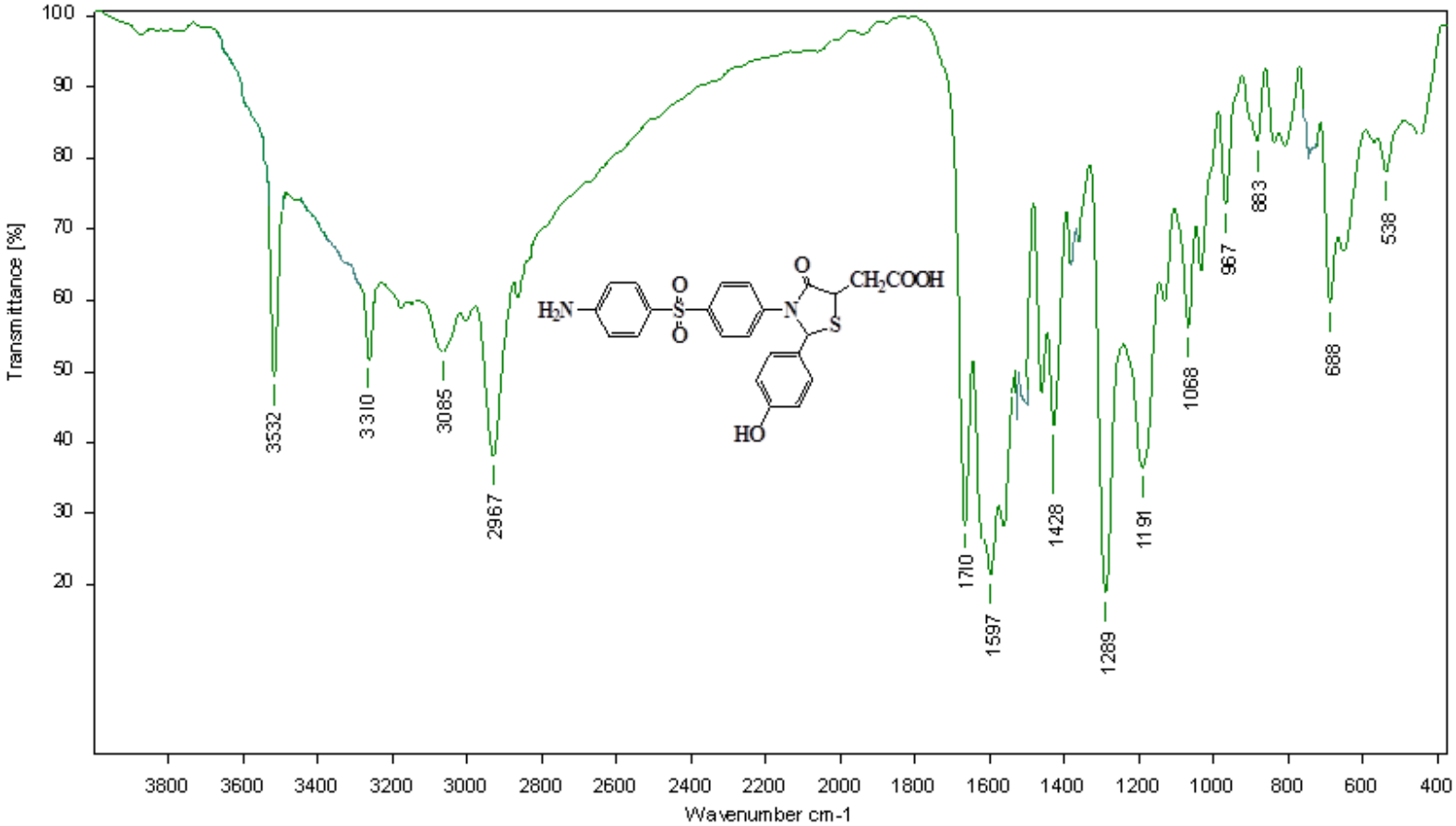
Sample Scans 16

Analyst name: Jayaseelan

JKK Nataraja College of Pharmacy
Kumarapalayam

3/14/2017 2:38:26 PM

Compound Name: TD4



(3-(4-(4-aminophenylsulfonyl) phenyl)-2-(4-hydroxyphenyl)-4-oxothiazolidin-5-yl)acetic acid (TD 4).

Experiment TRANS.xpm

Path of File C:\Program Files\OPUS_65\MEAS

Operator Name Administrator

Date of Measurement 14/03/2017

Instrument Type Alpha

Sample Form solid

Resolution 4

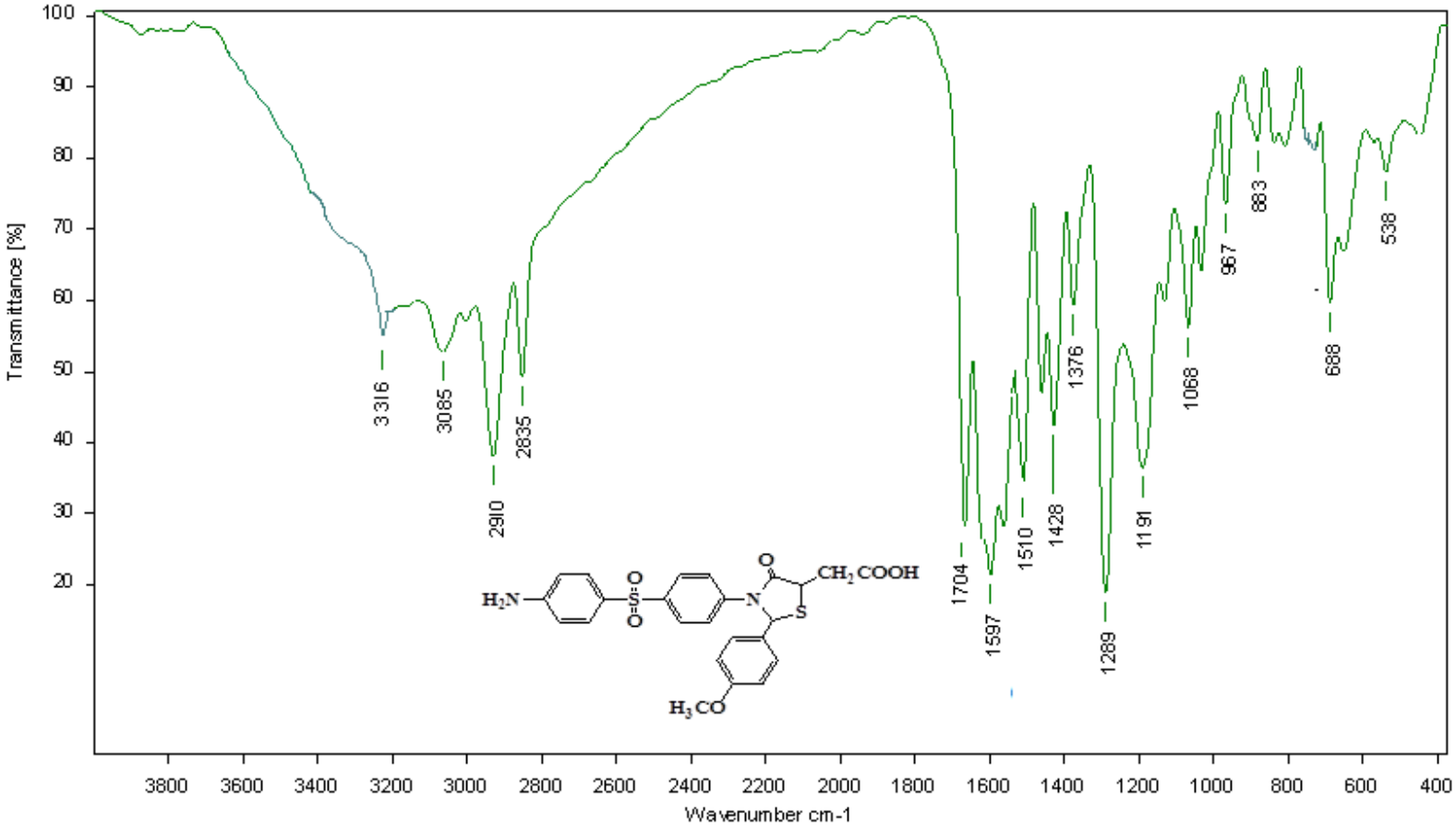
Sample Scans 16

Analyst name: Jayaseelan

JKK Nataraja College of Pharmacy
Kumarapalayam

3/28/2017 2:50:26 PM

Compound Name: TD3



3-(4-(4-aminophenylsulfonyl)phenyl)-2-(4-methoxyphenyl)-4-oxothiazolidin-5-yl)acetic acid (TD 3)

Experiment TRANS.xpm

Path of File C:\Program Files\OPUS_65\MEAS

Operator Name Administrator

Date of Measurement 28/03/2017

Instrument Type Alpha

Sample Form solid

Resolution 4

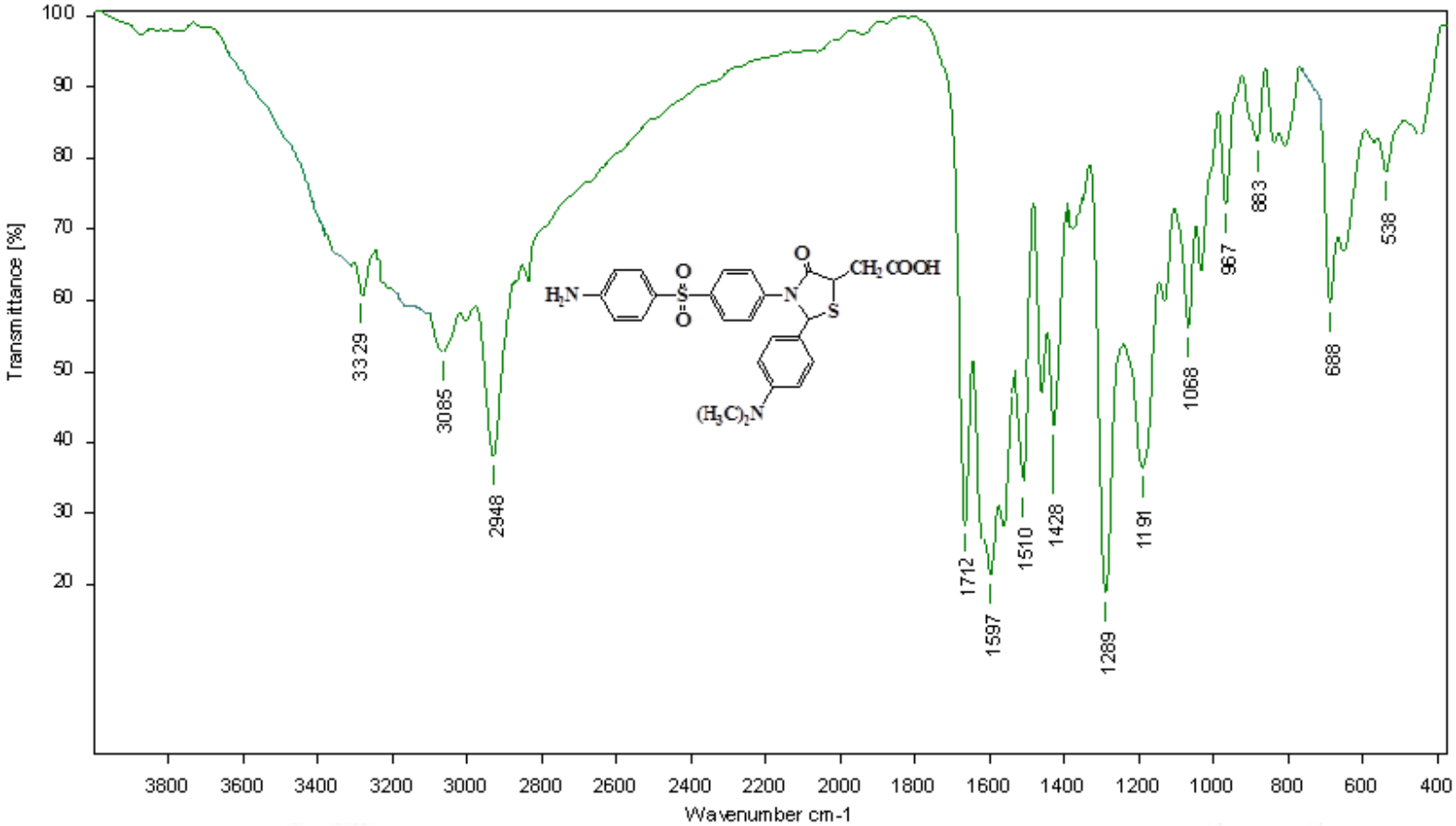
Sample Scans 16

Analyst name: Jayaseelan

JKK Nataraja College of Pharmacy
Kumarapalayam

5/28/2017 2:32: 50 PM

Compound Name: TD2



3-(4-(4-aminophenylsulfonyl)phenyl)-2-(4-(dimethylamino)phenyl)-4-oxothiazolidin-5-yl)acetic acid (TD2)

Experiment TRANS.xpm

Operator Name Administrator

Instrument Type Alpha

Resolution 4

Path of File C:\Program Files\OPUS_65\MEAS

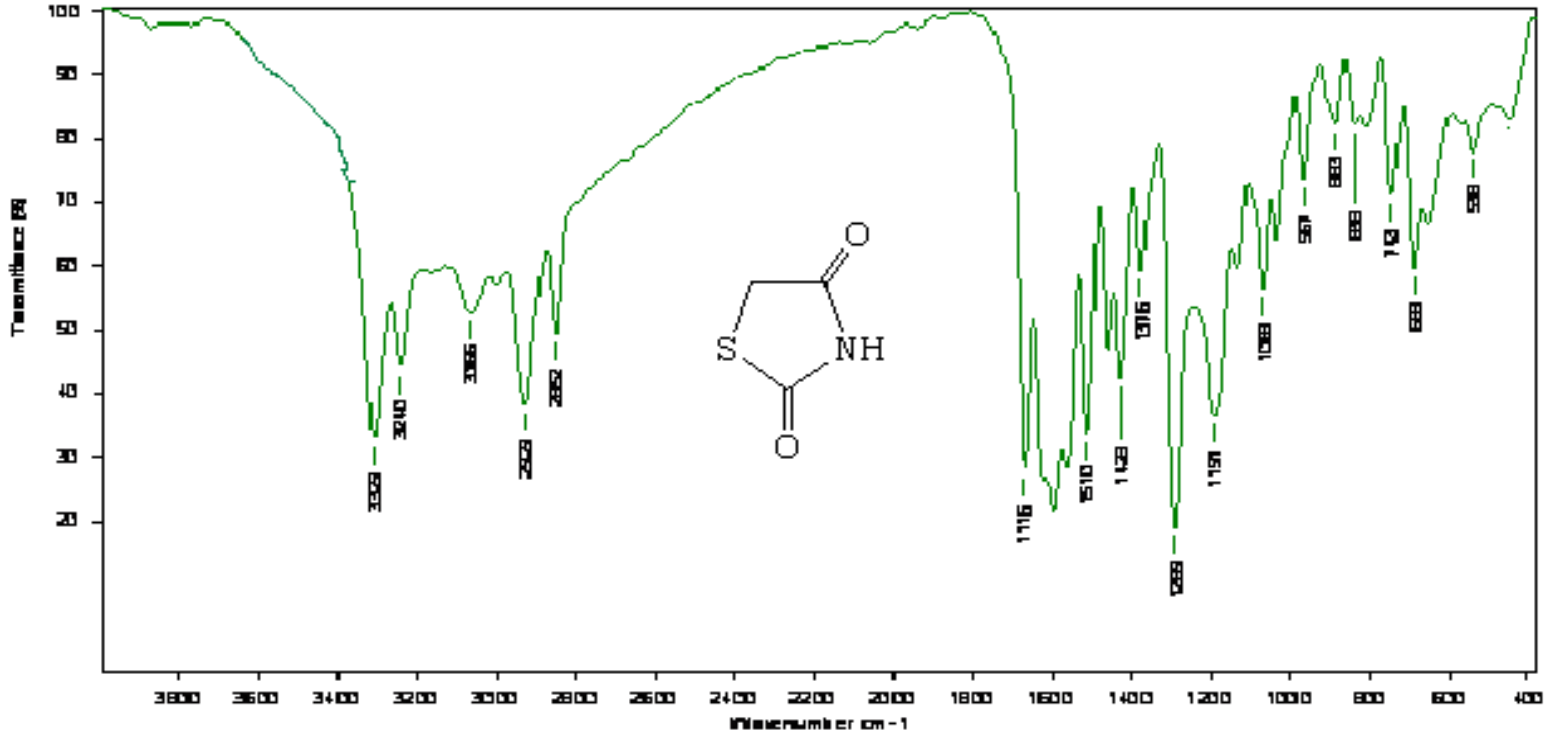
Date of Measurement 28/05/2017

Sample Form solid

Sample Scans 16

Analyst name: Jayaseelan

Compound Name: 2,4-Thiazolidinedione



thiazolidine-2,4-dione

Experiment: TRA 88.asm

Operator Name: Administrator

Instrument Type: Alpha

Resolution: 4

Analysis Frame: Sample scan

Pathname: C:\Program Files\OPUS_65\MEAS

Date of Measurement: 2/9/2009

Sample Form: solid

Sample Scans: 16

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